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c — correspondence  
cr — case record  
e — editorial

MMS — Massachusetts Medical Society  
mp — medical progress  
misc — miscellany

n — notice  
o — obituary  
\* — original article

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## THE WATERHOUSE-FRIDERICHSEN SYNDROME

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THE Waterhouse-Friderichsen syndrome is a clinical entity first described in 1911 by Waterhouse<sup>1</sup> in an eight-month-old child. In 1918, Friderichsen<sup>2</sup> reviewed the literature and described a similar case with a fulminating course, characterized clinically by stupor, cyanosis, pallor, vomiting and a rapidly spreading purpuric eruption, and at autopsy by massive bilateral adrenal hemorrhages. This syndrome is associated with a bacteremia, the etiologic agent in the majority of cases being the meningococcus. Although the pneumococcus, hemolytic streptococcus and staphylococcus have also been incupated, considerable doubt has been cast on the role of any of these organisms as the offending agent.

Most of the cases have occurred in children, but with the recent and widespread increase in meningococcal infections there have been many additional reports of this syndrome in adults.<sup>3-5</sup> Although in the majority of reported cases the patients succumbed within twenty-four hours of onset, a few survived for as long as forty-eight hours. Recently, 2 cases with survival periods of eighty and eighty-eight hours both proved by autopsy, were described.<sup>6</sup> Evidently this syndrome is not universally fatal, for there are 6 cases of recovery on record.<sup>7-12</sup>

We have observed 6 cases of the Waterhouse-Friderichsen syndrome — 5 with a fatal outcome and 1 with recovery — in a large series of meningococcal infections encountered at a station hospital. This presentation is an attempt to correlate the clinical, pathological and laboratory data obtained in these cases. The literature on recovery from this syndrome will be reviewed, and an additional case will be presented in detail.

### CLINICAL FEATURES

The clinical manifestations of the Waterhouse-Friderichsen syndrome have not been generally recognized. The paucity of clinical investigations is probably due to several factors, namely, failure in diagnosis, a fulminating course and the scarcity of cases seen by any one observer. The increasing prevalence of meningococcal infections has focused the attention of clinicians on this syndrome, and

it is reasonable to suppose that it will be recognized more frequently in the future. The clinical features of our 5 fatal cases have been so similar as to warrant detailed discussion. The case with recovery varied slightly from the others and will be described separately.

The prodromal symptoms were similar to those encountered in any respiratory infection, consisting of headache, chilly sensations, muscular pains and malaise. The onset of the bacteremia was sudden and dramatic. The most striking features were the profound shock and the petechial eruption, which in the course of a few hours became purpuric. The skin lesions varied in size from small petechiae several millimeters in diameter to large, violaceous purpuric areas widely distributed over the body. They did not disappear on digital pressure, and in some cases necrosis and sloughing followed in the later stages. The patients were apprehensive and restless. Despite an initial temporary delirium, mental lucidity was maintained throughout. There was pallor of the face and trunk. In addition, a nephritic type of facial edema was present. The lips and extremities were cold and cyanotic. Perspiration was profuse. Vomiting, persistent diarrhea and abdominal pain were frequent complaints.

The temperature was moderately elevated early in the disease, ranging from 100 to 102°F., but within twenty-four to thirty-six hours it dropped to normal and remained at normal or slightly subnormal levels until death. The pulse rate was accelerated throughout. The respirations were rapid and shallow during the initial shock, but with recovery from it they became slower and deeper. Twenty-four hours before death they rose sharply, averaging 48 per minute. Of particular interest is the fact that respirations ceased a few minutes prior to the failure of heart function.

Early in the disease, hypotensive blood-pressure levels were encountered. Frequently diastolic readings were unobtainable. With recovery from the initial shock the blood pressure rose to quasi-normal levels.

Soon after the onset, a few scattered moist rales were audible at both lung bases. This condition

gradually progressed until numerous coarse, bubbling rales could be heard over both lung fields. With the appearance of frank pulmonary edema terminally, the patient lapsed into coma and died shortly thereafter.

Remarkably little attention has heretofore been paid to the initial anuria, which was a constant finding in these cases. The anuria persisted for twenty-four to thirty-six hours and was replaced by a severe oliguria. At no time was adequate renal

nonprotein nitrogen level. In 3 cases, this finding was observed within twelve hours of onset and ranged between 52 and 64 mg. per 100 cc.; in 1 case, the blood was examined terminally. In all cases, the nonprotein nitrogen rose steadily, 96.9 mg. being the highest recorded level. Associated with this change was an early elevation of the blood creatinin, the concentrations varying between 5.4 and 9.0 mg. It is worthy of comment that the elevation of the nonprotein nitrogen was moderate, whereas that of

TABLE 1. *Laboratory Features.*

CASE No	CULTURE		BLOOD PRESSURE mm Hg.	UPINE	WHITE-CELL COUNT	BLOOD CHEMICAL FINDINGS*						OUTCOME
	BLOOD	SPINAL FLUID				CHLORIDE mg /100cc.	NONPROTEIN NITROGEN mg /100cc.	CREATININ mg /100cc.	ICTERIC INDEX	SODIUM mg /100cc.	POTASSIUM mg /100cc.	
1	+	+	0/0	Anuria	33,000							Death (2 hr)
2	+	-	90/60	Anuria								Death (13 hr)
3	+	+	52/22 initially and 102/62 terminally	Anuria followed by oliguria; incontinence.	73,150	454 470	46 67	5.8 9.0	13.7	373 403	10.2 10.0	Death (40 hr)
4	+	-	60/40 initially and 82/60 terminally	Anuria followed by oliguria, specific gravity 1.008 and 1.010, albumin +; microscopic examination negative.	47,250		86					Death (80 hr)
5	++	-	60/40 initially and 120/70 terminally	Anuria followed by oliguria; albumin ++; 50-60 red cells per high-power field, and hyaline and granular casts	66,950	412	52 91 96.9	7.0 7.4				Death (88 hr)
6	+	+	68/0 initially	Anuria (41 hours) followed by return of renal function; specific gravity 1.010, 1.001 and 1.020; albumin +; microscopic examination negative	49,350	396 412 479	64 70 78 50	5.4 4.7 3.6 3.2	6.0	345 324 271	16.9 19.8 12.8	Recovery

\*Blood samples for clinical readings in Cases 3, 5 and 6 were taken on successive days after admission.

†Meningococcus found on routine peripheral blood smear

function re-established, despite recovery from shock, evidenced by normal blood-pressure readings, the improved character of the pulse and the improved clinical appearance of the patient.

#### LABORATORY DATA

No significant biochemical studies of the Waterhouse-Friderichsen syndrome have hitherto been reported. We have therefore devoted some attention to the study of electrolyte balance and renal function. The data in all 6 cases are summarized in Table 1.

The blood chemical changes were investigated in 4 cases. All the patients exhibited elevation of the

the creatinin was marked. The icteric index showed a slight elevation to 13.7 in one of the fatal cases (Case 3). In contrast, the patient in Case 6, who recovered, had an icteric index of 6.0. In 3 cases (Cases 3, 5 and 6), the blood chloride levels were within normal limits.

In 2 patients (Cases 3 and 6), sodium and potassium determinations were done. Both showed slight sodium retention — 403 and 345 mg., respectively (normal, 315 to 340 mg.). In the case with a fatal outcome, the sodium continued to rise; in the recovered case, on the other hand, it dropped to a subnormal concentration. In the former the potassium was low, — 10 mg. (normal, 16 to 22 mg.), — where-

as in the latter it was normal. With recovery, however, the blood potassium also fell to a subnormal level.

A marked leukocytosis was observed in 5 cases, a blood-cell count being obtained in the other case. The white-cell count varied between 33,000 and 73,150, with a substantial increase in neutrophils. Although in some cases the initial counts were only moderately elevated, they invariably exhibited extreme leukocytosis during the subsequent twenty-four hours.

Urinalysis was done in all cases from which specimens could be obtained. Fixation of the specific gravity, and varying degrees of albuminuria, were noted. Interestingly enough, Case 4 demonstrated, in addition, a microscopic hematuria and cylindruria.

*Neisseria intracellularis* was cultured from the

in detail. Since these observations have an obvious bearing on the subject of this paper, the previous studies have been extended to include the remaining cases of the syndrome. Post-mortem examinations were performed in all the fatal cases (Table, 2). In evaluating these findings, it must be stressed that there is a vast difference in the morphologic structure of the liver, kidney and heart in short-lived cases as compared with that of those with longer survival periods.

The lungs revealed pleural effusion and pulmonary edema.

The adrenal glands were enlarged, varying in weight between 11 and 26 gm. Hemorrhagic areas were present bilaterally in the cortex and medulla. The shortest-lived cases (Cases 1, 2 and 3) showed the most extensive interstitial hemorrhages. It is

TABLE 2. Pathologic Features.

CASE No	LUNGS	HEART*	ASCITIC FLUID cc	LIVER	KIDNEYS	ADRENAL GLANDS
1	Pleural effusion (500 cc), pulmonary edema	Weight 300 gm; cloudy swelling of muscle fibers	None	Weight 1690 gm, mild hepatitis of central zone	Weight, 160 gm left and 160 gm right; normal histologically	Weight, 16 gm, severe bilateral hemorrhages
2	Pleural effusion (scant), pulmonary edema	Weight 370 gm, cloudy swelling of muscle fibers	None	Weight 1960 gm, mild hepatitis of central zone	Weight, 140 gm left and 135 gm right, normal histologically	Weight, 11 gm, severe bilateral hemorrhages
3	Pleural effusion (250 cc right, and 100 cc left), pulmonary edema	Weight 350 gm, pericardial effusion (100 cc), cloudy swelling and fragmentation of muscle fibers and interstitial edema	None	Weight 1950 gm, early necrosis of central zone	Weight, 145 gm left and 160 gm right, increased cellularity and avascularity of glomerular tufts, cloudy swelling of convoluted tubular epithelium, and albuminuous casts	Weight 26 gm, moderate bilateral hemorrhages
4	Pleural effusion (200 cc right and 200 cc left), pulmonary edema	Weight 410 gm, pericardial effusion (50 cc), same as Case 3 but severer	1000	Weight 2035 gm, dissociation of liver cords in central zone and severe necrobiosis of hepatic cells in central zone and midzone	Weight, 170 gm left and 185 gm right, histologically same as Case 3 but severer.	Weight, 15 gm, moderate bilateral hemorrhages
5	Pleural effusion (500 cc right and 75 cc left), pulmonary edema	Weight 590 gm, pericardial effusion (75 cc), same as Case 3 but severer	500	Weight 2790 gm; dissociation of liver cords, severe necrobiosis in central zone and midzone and early necrosis of hepatic cells in peripheral zone	Weight, 280 gm left and 240 gm right, histologically same as Case 3 but severer	Weight, 20 gm, moderate bilateral hemorrhages

\*All cases except Case 1 revealed dilatation of the right auricle and ventricle

blood of each case. Despite grossly and microscopically negative spinal fluids, the cultures in 3 cases were positive.

#### PATHOLOGICAL FINDINGS

Characteristic morphologic changes do exist in the Waterhouse-Friderichsen syndrome. Failure to recognize these structural variations may be attributed to the fact that such changes are progressive and become well defined only in those cases that have a prolonged clinical course. In reviewing the literature, we were impressed by the reports of the unusual brevity of this syndrome, the majority of patients succumbing within twenty-four hours, with an occasional survival period of forty-eight hours. In a previous publication we<sup>6</sup> reported 2 proved cases with prolonged survival periods and discussed the characteristic pathological features

evident from these observations that the length of survival is determined by the severity of destruction of adrenal tissues.

The livers were enlarged, weighing between 1950 and 2790 gm, except for that in Case 1, which weighed 1690 gm. The largest livers were seen in Cases 4 and 5, which had the longest survival periods. The microscopic changes varied in direct proportion to the survival time. In the shortest-lived cases (Cases 1 and 2), the sole finding was a mild hepatitis of the central zone. In Case 3, in which the patient survived for forty hours, an early necrosis of the central zone was present. In Case 4, with a survival time of eighty hours, there was dissociation of the liver cords of the central zone, with severe necrobiosis of the hepatic cells, midzonal necrobiosis and vacuolization of the hepatic cells, and a normal peripheral zone. However, Case 5, with a survival

period of eighty-eight hours, revealed similar although severer central and midzonal changes than did Case 4 and, in addition, early necrobiosis of the cells in the peripheral zone.

The kidneys were enlarged in only 2 cases (Cases 4 and 5), in which together they weighed 355 and 520 gm., respectively. The histologic architecture in Cases 1 and 2 was normal. In Cases 3, 4 and 5, with clinical courses of forty, eighty and eighty-eight hours, respectively, the microscopic features, although similar to one another, again were severest in the cases with the longest survivals. These consisted of increased cellularity and avascularity of the glomerular tufts, cloudy swelling of the proximal convoluted tubular epithelium and albuminous deposits in the tubular lumens. It therefore seems justifiable to conclude that significant renal changes are found only in those cases with prolonged survival periods.

The heart was grossly abnormal in 4 of the 5 fatal cases (Cases 2, 3, 4 and 5). These abnormalities consisted of cardiac hypertrophy, with the weight varying between 350 and 590 gm., and with marked dilatation of the right auricle and right ventricle. Pericardial effusion occurred in Cases 3, 4 and 5. No noteworthy gross changes were present in Case 1, in which the patient survived for two hours. The myocardium in all 5 cases revealed microscopic findings of a nonspecific character and were similar to those found in other infectious diseases and septicemias. Cloudy swelling was observed in all cases, but in addition, Cases 3, 4 and 5 disclosed fragmentation of the muscle fibers and interstitial edema. These degenerative changes were most advanced in the cases with the longest clinical courses.

The lungs, liver, spleen, kidneys and brain exhibited severe congestion. Petechiae were distributed over the serous membranes, gastrointestinal tract and heart — subendocardium, epicardium and papillary muscles. Pleural, pericardial and peritoneal serous effusions were found that clotted spontaneously. In only 1 case (Case 3) was a purulent inflammation of the meninges present.

#### DIAGNOSIS

It is appropriate at this point to consider the diagnostic problem posed by the Waterhouse-Friderichsen syndrome. Since the incidence of this entity is constantly rising, the necessity for uniform criteria can hardly be disputed. From a survey of the foregoing material, there have been gathered clinical and laboratory data on which a diagnosis of this syndrome can be based. The following points are regarded to be of diagnostic significance: petechial eruption rapidly becoming purpuric; severe shock; facial edema; anuria of twenty-four to thirty-six hours' duration, followed by marked oliguria; urinalysis showing fixation of the specific gravity, albuminuria, hematuria or cylindruria; marked

leukocytosis; isolation of the meningococcus by culture and, in some cases, by peripheral blood smear; renal failure, as evidenced by elevation of the blood nonprotein nitrogen and creatinin; and elevation of the blood sodium and diminution of the blood potassium.

A diagnosis of this syndrome cannot be based solely on any isolated factor mentioned above. On the basis of these studies it is concluded that the clinical signs per se are sufficient to warrant the diagnosis in acute, fulminating cases. With a more prolonged course, however, additional factors involving the alterations in blood chemistry, as well as the isolation of the meningococcus, must be consistently present to confirm the diagnosis.

#### TREATMENT

The therapeutic approach in the Waterhouse-Friderichsen syndrome resolves itself into the treatment of shock, toxemia and bacteremia and the administration of adrenocortical hormone substitution therapy.

Shock is combated in the usual manner. The employment of heat and stimulants and the antishock position are advocated. Parenteral fluids in quantities of 3000 to 4000 cc. should be given cautiously over a twenty-four-hour period. The intravenous administration of 500 cc. of plasma, repeated in twelve hours, is recommended because of its osmotic effect, mirrored in a noticeable elevation of the blood pressure. The use of epinephrin, in our experience, is of questionable value.

Toxemia is the gravest problem encountered in this entity, and the pathologic changes are directly attributable to it. Although at the present time there is no clear evidence that serotherapy is of value in meningococcal infections, it seems advisable to administer antimeningococcus serum in adequate amounts — 60,000 to 120,000 units — intravenously within the first twenty-four hours.

The control of meningococcemia has been made possible by the advent of chemotherapy. Of all the sulfonamide drugs, sulfadiazine is the derivative of choice. The necessity for massive doses of this drug, parenterally and orally, is apparent when one considers the overwhelming character of the bacteremia. The initial dose of sulfadiazine in this series was 5 gm. intravenously and 8 gm. orally. This was followed by large oral doses until a total of 25 to 30 gm. had been given within the first twenty-four hours. The blood-sulfadiazine concentration was used as a guide for determining the size and frequency of subsequent doses. The optimal blood level was considered to be 15 to 20 mg. per 100 cc.

The rationale of adrenocortical hormone substitution therapy in the Waterhouse-Friderichsen syndrome has been directed toward combating adrenal dysfunction resulting from the extensive hemorrhages and necrosis. The hope that this form of organotherapy would succeed in tiding the patient

over his critical period has met with disappointment. Experience indicates that its value is questionable. No resultant clinical improvement could be detected in the 4 cases in which it was used. Nevertheless, it may have contributed to the prolongation of the clinical course.

### RECOVERY

Only 6 cases of the Waterhouse-Friderichsen syndrome with recovery have been reported in the literature.<sup>7-12</sup> A review of these cases failed to reveal any uniform criteria for diagnosis. The meningococcus was the etiologic agent in 5 of these cases. The pneumococcus was isolated from the case reported by Bickel.<sup>7</sup>

The diagnosis of recovery in this entity must necessarily be based solely on the clinical findings and laboratory data, because no pathologic evidence is available. It must be emphasized that fulminating meningococcemia associated with shock may simulate the Waterhouse-Friderichsen syndrome, but in the former autopsy fails to disclose any adrenal hemorrhages. From our observations, it is concluded that the important clinical differentiation of these two types is that in meningococcemia with shock no anuria and oliguria or retention of nitrogenous products in the blood occurs, whereas they are consistently present in the Waterhouse-Friderichsen syndrome. The cases of Carey,<sup>8</sup> Peabody<sup>10</sup> and Rucks and Hobson<sup>11</sup> showed many features that are found in the above criteria for diagnosis, particularly the purpuric manifestations, shock, anuria and oliguria, leukocytosis and elevation of the blood nonprotein nitrogen level.

In a previous publication, we<sup>6</sup> maintained that recovery was unlikely because of the basic morphologic changes found at post-mortem examination in protracted cases. In retrospect, this statement should be modified, because a case with recovery has since been observed. It is believed that the bacteremia, toxemia and resulting adrenal hemorrhages are quantitative; that they may be lethal or sublethal can hardly be questioned. It is not inconceivable, therefore, that this triad with its train of pathologic changes may be mild to moderate and fully compatible with recovery.

The following case is presented in detail as an example of recovery from the Waterhouse-Friderichsen syndrome. Interestingly enough, the clinical course and laboratory findings were not unlike those in the case reported by Peabody.<sup>10</sup>

### CASE REPORT

An 18-year-old soldier was admitted to a station hospital complaining of headaches, nausea and pains in the neck and back. On admission the temperature was 102°F., the pulse 92, and the respirations 36. Physical examination was essentially negative except for coryza and a red, injected pharynx. Three hours later the patient became delirious and irrational. He vomited bile-stained fluid and passed frequent, involuntary watery stools. Petechiae were first observed at that time. The blood pressure was 60/0, and the pulse 150.

A lumbar puncture revealed clear spinal fluid under normal pressure, which was negative on laboratory examination. A white-cell count taken shortly after admission was 17,050, with 80 per cent neutrophils. A diagnosis of meningococcemia was made and treatment with 8 gm. of sulfadiazine by Levin tube was instituted. Subsequent sulfadiazine therapy consisted of 3 gm. every 3 hours. Parenteral fluids and 1 cc. of metrazol were administered intravenously.

The patient lapsed into a stuporous state 8 hours after entry. The temperature remained at 102°F. Examination disclosed slight facial edema. Numerous violaceous, petechial and purpuric areas were widely distributed over the trunk and extremities. Nuchal rigidity was absent. No abnormal neurologic signs could be elicited. The blood pressure was 68/0. A second white-cell count was 49,350, with 83 per cent neutrophils. The blood-sulfadiazine level was 13.8 mg. per 100 cc., and the blood chlorides 396 mg. Urinalysis could not be done because of complete anuria since admission. Blood and spinal-fluid cultures were positive for *Neisseria intracellulularis* (Type I). A diagnosis of severe meningococcemia complicated by adrenal hemorrhages (Waterhouse-Friderichsen syndrome) was made. Intensive sulfadiazine therapy was continued orally, and 5.5 gm. of sodium sulfadiazine dissolved in sterile distilled water was administered intravenously. In addition, 30,000 units of meningococcus antitoxin with 1 cc. of epinephrin and 5 cc. of adrenocortical hormone was given by intravenous drip and repeated 6 hours later.

On the 2nd hospital day, 28 hours following admission, the patient was clinically improved. He appeared rational and the blood pressure rose to 72/40. The temperature was 99.4°F., the pulse 70, and the respirations 18. Despite intensive administration of fluids, the anuria persisted. The urinary bladder could not be palpated. The patient continued to vomit and complained bitterly of diffuse abdominal pain and diarrhea.

He received 27 gm. of sulfadiazine during the first 24 hours of therapy. The white-cell count fell to 23,950, with 96 per cent neutrophils. Complete blood chemical studies were done and were reported as follows: nonprotein nitrogen, 64 mg.; creatinin, 5.4 mg.; sugar, 101 mg.; chloride, 412 mg.; sodium, 345 mg.; potassium, 16.9 mg.; and icterus index, 6.0. The blood pressure rose to 80/60.

Vigorous sulfonamide therapy was continued, and a dosage schedule of 3 gm., alternated with 2 gm., administered orally every 3 hours was initiated. A blood sulfadiazine level of 14.4 mg. per 100 cc. was reported at that time. Renal function was re-established 41 hours after admission, at which time the patient spontaneously voided 540 cc. of dark-amber urine, which had a specific gravity of 1.010 and showed a moderate trace of albumin and a few white cells.

On the 3rd day, facial edema and asthenia were still present. The temperature fluctuated between 100 and 102°F. The blood pressure continued to climb, reaching 100/78. Blood chemical determinations were repeated, with the following results: nonprotein nitrogen, 70 mg.; creatinin, 4.7 mg.; sodium, 324 mg.; and potassium, 19.8 mg. The blood sulfadiazine was maintained at a satisfactory concentration of 16.6 mg. The total fluid intake was 4120 cc., and the urinary output 1100 cc. The sulfadiazine was then reduced to 2-gm. doses, alternated with 1 gm., every 4 hours. Throughout the remainder of the first week, there was fixation of the urinary specific gravity at 1.010.

Definite improvement was observed on the 4th day. The asthenia was considerably lessened. The first laboratory findings to confirm the clinical impression of recovery were a fall in the creatinin level to 3.6 mg. and one in the sodium level to 271 mg., with a concomitant fall in the potassium level to 12.8 mg. The nonprotein nitrogen was reported as 78 mg., a slight rise over the previous level. The blood chloride continued to increase, having attained a level of 479 mg. The white-cell count was 24,750, with 96 per cent neutrophils. The blood-sulfadiazine level was 19.5 mg., representing a slight increase over the previous reading. The fluid intake and urinary output were 3840 cc. and 2640 cc., respectively.

On the 6th day, the facial edema had completely disappeared, the purpuric lesions had faded and the temperature returned to normal for the first time. The white-cell count was 14,000, with 80 per cent neutrophils. The nonprotein nitrogen dropped to a level of 50 mg., and the creatinin to 3.2 mg. The sulfadiazine was discontinued.

The clinical course from that time on was one of progressive improvement. The sole complicating feature was a

period of eighty-eight hours, revealed similar although severer central and midzonal changes than did Case 4 and, in addition, early necrobiosis of the cells in the peripheral zone.

The kidneys were enlarged in only 2 cases (Cases 4 and 5), in which together they weighed 355 and 520 gm., respectively. The histologic architecture in Cases 1 and 2 was normal. In Cases 3, 4 and 5, with clinical courses of forty, eighty and eighty-eight hours, respectively, the microscopic features, although similar to one another, again were severest in the cases with the longest survivals. These consisted of increased cellularity and avascularity of the glomerular tufts, cloudy swelling of the proximal convoluted tubular epithelium and albuminous deposits in the tubular lumens. It therefore seems justifiable to conclude that significant renal changes are found only in those cases with prolonged survival periods.

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The rationale of adrenocortical hormone substitution therapy in the Waterhouse-Friderichsen syndrome has been directed toward combating adrenal dysfunction resulting from the extensive hemorrhages and necrosis. The hope that this form of organotherapy would succeed in tiding the patient

may well account for the degenerative changes found in the liver, kidneys and heart.

### SUMMARY AND CONCLUSIONS

A report is made of 6 cases of the Waterhouse-Friderichsen syndrome. Criteria for diagnosis based on an analysis of these cases are presented. A case of recovery is discussed in detail, and the literature on recovery in this syndrome is reviewed.

The following conclusions are based on a study of these cases:

The clinical features are fairly constant. The significance of the renal failure as evidenced by the initial anuria followed by oliguria has heretofore not been fully appreciated.

The pathologic findings are uniform but vary in degree. All cases have macroscopic bilateral adrenal hemorrhages. Microscopically the changes in the heart, liver and kidneys are not conspicuous in the short-lived cases but are pronounced in those cases with relatively long clinical courses.

The roles of bacteremia and shock in pathogenesis have been overemphasized. Death in all cases is probably the effect of the overwhelming tox-

emia, which in the short-lived cases results in profound shock and in those with relatively long survival periods leads to hepatorenal failure.

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## TRANSITORY LUNG INFILTRATIONS ACCOMPANIED BY EOSINOPHILIA

### Report of a Case

CAPTAIN HENRY MILLER, M.C., A.U.S.

THE clinical aspects of any disease may be said to comprise a group of features that in the aggregate tend to classify it as a clinical entity. Some diseases have certain pathognomonic features that identify them immediately, whereas in others the clinical picture is simulated by such a variety of etiologic agents that it is impossible to be certain of the diagnosis except by careful study and the elimination of similar diseases. Such a condition is the syndrome of transient pulmonary infiltrations with blood eosinophilia, first described in 1932 by Loeffler,<sup>1</sup> professor of medicine at the University of Zurich. By 1940, 105 cases had been reported in the literature;<sup>2</sup> 51 of them by Loeffler.<sup>3</sup>

The most important criteria for diagnosis are the symptoms and signs of pulmonary disease, the extent and character of pulmonary involvement, the transient character of the pulmonary shadows, eosinophilia, and seasonal and sex variation. These will now be discussed. The symptoms as a rule are few, and the course is mild and invariably benign. The majority of patients do not appear to be acutely ill. Over 25 per cent of Loeffler's cases were discovered accidentally. There is rarely any appreciable rise of temperature. A cough, with or without chest pain and expectoration of frothy, mucoid sputum, may be present. Abnormal physical signs

over the lungs are few, and in general consist of occasional moist rales. Sometimes impairment of the percussion note and changes in breath sounds are elicited. The sedimentation rate is usually increased.

X-ray examination usually reveals a more extensive pulmonary involvement than was suspected from the clinical examination. The characteristic x-ray picture described by Loeffler and also by Breton<sup>4</sup> consists of abnormal shadows that appear and disappear rapidly, only to reappear in another portion of the lung. The involvement varies in size and position. It occurs most frequently in the lower lung fields but may occur anywhere. It may be small or large, unilateral or bilateral, single or multiple and homogeneous or spotty. A fine, fibrous, star-shaped scar may be left after resolution. Occasionally there is a small pleural effusion, but it is never large enough to warrant thoracentesis. The pulmonary shadows decrease in size and density in three to eight days, and completely disappear within a few more days. Other shadows may appear in different regions of the lungs in rapid succession.

The eosinophilia usually ranges between 15 and 35 per cent, but has in some cases exceeded 60 per cent. It is associated with the lung shadows, but



temporary exhaustion and delirium state that occurred on the 17th day, characterized by depression, auditory and visual hallucinations and a recurrence of the asthenia that lasted for 6 days. The patient made a complete recovery and was discharged to his unit 46 days after hospitalization. Subsequent examinations showed no sequelae, and the patient was able to resume full military duties.

The clinical course in this case was similar to that in the 5 fatal cases, but differed from it in that renal function was restored and an elevated temperature was maintained. The re-establishment of renal function heralded recovery and was the most important prognostic sign. The rise in the non-protein nitrogen and the creatinin occurred early in the course of the illness.

### DISCUSSION

Although cognizant of differences of opinion, we are inclined to agree with Martland<sup>4</sup> and Herbut and Manges<sup>13</sup> that the meningococcus is the sole etiologic agent in the Waterhouse-Friderichsen syndrome. The evidence that substantiates this claim is the increased prevalence of this syndrome during epidemics of meningitis and the frequent recovery of the meningococcus. This organism has been found in many isolated cases in which the etiology was obscure. The meningococcus was cultured in the 6 cases of the Waterhouse-Friderichsen syndrome encountered in this series. We strongly doubt the primary role ascribed to other micro-organisms and support the concept that they represent secondary invaders.<sup>13</sup>

It is now a well-established fact that the meningococcus obtains its initial hold in the nasopharynx, from which it rapidly invades the blood stream. If adrenal hemorrhages occur, the classic picture of the Waterhouse-Friderichsen syndrome results and is manifested by bacteremia, shock and toxemia. Each of these factors forms the basis of a theory that attempts to explain the pathogenesis of this syndrome. It need scarcely be pointed out that the presence of bacterial organisms in the blood cannot per se adequately explain the adrenal hemorrhages and associated clinical evolution, because the Waterhouse-Friderichsen syndrome does not invariably follow every meningococcemia or other bacteremia. A further objection to the bacteremic theory is the failure in these cases to demonstrate pathologic lesions of a focal embolic type. Nor can shock alone explain the ensuing histologic picture. The major criticism of this concept and of the conclusions drawn is that observations were made in all instances on cases with brief clinical courses. Not until studies have been made on cases surviving the initial phase will one be justified in differentiating this early state of shock from the later and more fully developed toxemic state of hepatorenal failure. These studies have shown that the clinical features of shock, such as weakness, pallor, a thready pulse and low blood pressure, although present early in this syndrome, do disappear within six to eight

hours, provided that the patient survives. A terminal fall in blood pressure was observed. Notwithstanding clinical recovery from shock, which in itself was variable in severity and duration, alterations in the blood nonprotein nitrogen and creatinin continued to progress unfavorably. Furthermore, it was impossible to demonstrate hemoglobin concentration, hypochloremia or a fall in blood sodium and a rise in blood potassium, all of which are characteristic of shock. That the morphologic alterations in structure found in shock are strikingly similar to those found in the Waterhouse-Friderichsen syndrome cannot be questioned, but to attribute the pathologic changes in this syndrome to shock despite obvious clinical recovery from this state is untenable. Thus, the preponderance of evidence supports the principle of toxemia as the most important factor in the pathogenesis of the Waterhouse-Friderichsen syndrome. That shock may have been an early but temporarily associated factor in these cases cannot be denied. Rather, the emphasis must be placed on the toxins elaborated by the meningococcus, with its subsequent disorganization of the structure and function of the endothelial cells, and certain types of parenchymal cells. The endothelial cellular damage resulted in hemorrhage into the skin and adrenal glands, extravasation of fluid into the serous cavities and pulmonary edema. The parenchymatous changes, which were degenerative in nature and were found in the liver, kidney and heart, resulted in hepatorenal failure.

In the previous publication, we<sup>6</sup> showed the existence of two stages in the Waterhouse-Friderichsen syndrome. The first or fulminating stage was characterized by a short course and circulatory collapse. The pathologic changes were cloudy swelling of the myocardium and an early hepatitis associated with adrenal hemorrhages. Death was most readily accounted for by shock subsequent to the overwhelming toxemia. The second or hepatorenal stage was found only in the patients who survived for longer intervals, and its main histologic features were cloudy swelling with fragmentation of the myocardium, adrenal hemorrhages, a severe and widespread necrobiosis of the hepatic cells and cloudy swelling of the renal convoluted tubular epithelium, together with avascularity and increased cellularity of the glomeruli. Death in these cases was attributed to hepatorenal failure.

We believe that adrenal hemorrhages are necessary for the development of the Waterhouse-Friderichsen syndrome, although it is difficult to explain their exact role. Investigators have shown that the adrenal cortex plays an important part in the maintenance of renal function and body resistance to toxic agents. It is therefore suggested that the destruction of adrenocortical tissues by hemorrhage results in a failure of renal function and increased sensitivity to the meningococcal toxin. The latter

late stages of the myelocytic series. There was a distinct increase in the number of eosinophils.

On November 28, radiographic examination of the chest revealed increased hilar markings, with multiple small areas of increased density scattered through both lung fields (Fig. 1). On December 10, the x-ray films revealed resolution of the previously reported process, but an area of infiltration was present in the lower lobe of the right lung (Fig. 2). On Decem-

disease<sup>17</sup> may at times be associated with a hyper-eosinophilia, but in the present case these diseases can be definitely excluded by the clinical course. There was no means of ruling out familial eosinophilia.<sup>18</sup> There is a group of unusual cases with varying symptoms reported as "eosinophilic leu-

TABLE 1. Summary of Hematologic Findings.

DATE	HEMOGLOBIN	RED-CELL COUNT	WHITE-CELL COUNT	NEUTROPHILS	DIFFERENTIAL COUNT			SEDIMENTATION RATE (WESTERGRÉN)
	%	$\times 10^6$	$\times 10^3$	%	EOSINOPHILS %	LYMPHOCYTES %	MONOCYTES %	mm.
11/29			16.2	7	85	8		
12/2			18.8	10	76	14		
12/10			19.9	11	79	10		58
12/13	90	4.7	30.8	14	76	40		
12/16			24.7	11	76	13		
12/20								77
12/23			41.0	17	80	3		55
12/26			33.0	10	79	11		
12/29	95	5.0	27.7	11	82	7		
1/2			25.8	6	82	12		
1/7	90	4.5	21.1	17	64	19		
1/14			19.5	9	75	14	2	
1/17	85	4.25	19.6	14	76	10		65
1/21			21.9	14	69	17		
1/25			19.6	12	79	9		
1/31			22.5	11	72	16	1	
2/5	90	4.42	12.1	12	61	27		61
2/8			7.0	20	58	21	1	
2/13			6.7	31	36	33		
2/17			6.2	44	31	25		
2/24	105	4.95	5.6	76	2	20	2	15

ber 26, there was almost complete resolution of the pneumonic process at the right base, with some residual thickening of the interstitial structures in this region (Fig. 3). A film

kemia," but this disease resembles a genuine leukemia in that the spleen is greatly enlarged, the num-



FIGURE 1.



FIGURE 2.

on January 9 revealed clear lung fields. X-ray films of the skull and the long bones revealed no abnormalities. The patient eventually returned to active duty.

#### DISCUSSION

With regard to the differential diagnosis, it is to be noted that periarteritis nodosa<sup>16</sup> and Hodgkin's

ber of leukocytes is markedly increased, there is a tendency to hemorrhage, and the outcome is uniformly fatal.<sup>19</sup> In 1931, Bass<sup>20</sup> reported a case that was diagnosed as eosinophilic leukemia. X-ray examination revealed generalized speckled shadows throughout both lung fields, which suggested miliary

Loeffler found no parallelism between the degree of eosinophilia and the extent of the infiltrations. There appears to be a definite seasonal variation, most cases being found in July and August; furthermore, males are more frequently affected than are females.

The pathology of this disease is unknown, since no clear-cut fatal case has come to autopsy. In 1939, Smith and Alexander<sup>5</sup> reported a fatal case of so-called "Loeffler's syndrome" in a seven-year-old girl. As brought out in the discussion, the high fever, stormy course, long duration and fatal outcome did not fit into the picture of a true Loeffler's syndrome. In addition, none of five nationally known pathologists could agree on the diagnosis. Terminal leukemia was granted by one and questioned by the other four.

The etiology of the disease is also uncertain. Most authorities describe the syndrome as an allergic response of the pulmonary tissue that may be induced by various allergens. Loeffler recognized the probable presence of multiple etiologic factors. Leitner<sup>6</sup> associated the condition with pulmonary tuberculosis. Wild and Loertscher<sup>7</sup> reported 2 cases of the syndrome in children infected with *Ascaris lumbricoides* and explained the pulmonary shadows as due to the passage of the larvae through the lungs. Engel<sup>8</sup> described a similar clinical picture of transient pulmonary infiltration and blood eosinophilia in himself and a friend, and attributed the condition to hypersensitivity to the pollen of the privet plant. In 1937, Meyer<sup>9</sup> reported 8 cases, including one that developed sudden rhinitis, conjunctivitis and edema of the face, accompanied by eosinophilia and lung infiltration. All these manifestations disappeared with calcium therapy and removal of contact to a pollen to which the patient gave a strongly positive reaction. Since then, other investigators have reported transient lung shadows in asthmatic patients and have decided that an allergic process is probably responsible for the entire picture. Although asthma is the most frequently associated allergic manifestation, other forms of allergy have been noted.

Stefano<sup>10</sup> reported a case of bronchial asthma in which transient areas of pulmonary infiltrations demonstrable by x-ray were associated with amebas in the sputum. Both the asthma and the amebas disappeared after emetine therapy. Hoff and Hicks<sup>11</sup> have also reported a case of Loeffler's disease associated with amebiasis. Quintana<sup>12</sup> described a case in which *Necator americanus* was present in the stools. Lavier, Bariety and Caroli<sup>13</sup> have described a case of pulmonary infiltration with eosinophilia in a case of infestation with *Fasciola hepatica*. In the great majority of cases, no etiologic agent has been found.

The following case is reported because of the apparent rarity of the condition. A review of the

literature reveals but 4 such cases reported in this country.<sup>2, 11, 14, 15</sup>

### CASE REPORT

A 23-year-old soldier was admitted to the hospital on November 27, 1943. For several days prior to admission he had noticed unusual shortness of breath on moderate exertion. This was particularly evident when he ran up an embankment to his gun position. On November 26, he developed a sore throat, fever, generalized malaise and aching of the bones and muscles. On the morning of the 27th, he developed a shaking chill that lasted for 2 hours. On the day after admission, he developed a nonproductive cough associated with a dull, aching pain in the left side of the chest. He gave no history of hemoptysis, pleurisy or weight loss, and no family history of tuberculosis. Careful questioning revealed nothing suggestive of allergy in the family or past history. There were no symptoms referable to the gastrointestinal or genitourinary system.

On admission, the temperature was 100°F., the pulse 84, and the respirations 20. The pharynx was granular and moderately injected. The lungs were resonant throughout. On auscultation numerous rhonchi were heard throughout both lung fields, being most marked at the bases posteriorly. No moist rales were noted. The area of cardiac dullness was not enlarged, the rhythm was regular, and no murmurs were heard. The aortic second sound was equal to the pulmonic. The blood pressure was 114/78. The abdomen was soft, and no organs or masses were felt.

The temperature dropped to normal in 24 hours, and the patient remained afebrile throughout the hospital stay. The pulse varied between 60 and 78, and the respirations were 20. On the 9th hospital day, the cough became productive of gradually increasing amounts of frothy, whitish, mucopurulent sputum, which eventually totaled 30 to 60 cc. a day. This persisted for 2 weeks and then gradually decreased, so that after 4 weeks the cough and expectoration of sputum ceased. On December 14, examination revealed diminished resonance at the right base, with numerous fine, moist rales at both lung bases posteriorly. The rales gradually decreased, and, on December 31 the lungs were clear on physical examination. The patient did not appear acutely ill at any time, and treatment for the most part was symptomatic. He received two doses of 3 cc. each of tetrachlorethylene and two courses of 1 gm. each of hexylresorcinol crystals, following which the ova of *Trichuris trichiura* (see below) disappeared from the stools. On January 20, he was started on 0.015 gm. of Mapharsen; this was followed by biweekly injections of 0.06 gm. of the drug for ten doses.

Repeated urinalyses were normal. Concentrated specimens revealed no evidence of ova or parasites in the sediment. Thirty-two stool examinations were negative for the ova of *N. americanus*, *Schistosoma mansoni* and *A. lumbricoides* and cysts and trophozoites of *E. histolytica*. On January 18 and 26, an occasional ovum of *T. trichiura* was found in the stool. Twenty-six sputum examinations revealed no evidence of tubercle bacilli, fungi, ova or parasites; a culture revealed *Staphylococcus aureus*. From December 9 to 18, examinations revealed a moderate to marked increase of eosinophils in the sputum.

Tuberculin tests were negative. An electrocardiogram was normal. Between January 13 and 15 the patient was skin-tested with twenty-four common allergens, with completely negative results. A sigmoidoscopic examination to a depth of 37 cm. revealed the bowel mucosa to be normal throughout, no hemorrhagic areas being seen. Agglutination tests and the brucellergen intradermal test for brucellosis were negative. An intradermal test with trichinella antigen was likewise negative.

Numerous thick blood films were negative for malarial and other parasites. Three midnight blood smears were negative for filariasis. Repeated examinations of blood smears revealed no abnormality of the erythrocytes. The eosinophils in the blood varied from 64 to 85 per cent during the first two months and had returned to normal (2 per cent) at the end of the third month (Table 1). The eosinophils were adult if judged by the nuclei, which were multilobed. On December 27, smears of the sternal marrow revealed it to be predominantly myeloid, and the elements present were of the

infiltration. These findings were not transitory. Repeated examinations over a period of six months revealed no significant changes. Diffuse pulmonary infiltration, fever and eosinophilia have been reported in chronic brucellosis,<sup>21</sup> but in the present case the agglutination reaction and a skin test for brucellosis were negative. Trichinosis, which may have respiratory abnormalities as a significant feature of the disease,<sup>22</sup> is rare in this locality, and could be excluded by the clinical course and negative skin test.



FIGURE 3.

Other tropical diseases characterized by blood eosinophilia were excluded by clinical and laboratory studies. Although trichuriasis may at times be associated with urticaria and a moderate eosinophilia, it is doubtful whether it was a significant etiologic factor. Recently, Weingarten<sup>23</sup> in India described what he believes to be a new clinical entity, manifested by severe, paroxysmal bronchitis and a high eosinophilia, in which arsenicals are a specific and quickly acting remedy. The disease is characterized by a paroxysmal cough, expiratory dyspnea and occasional attacks of bronchial asthma, with mucopurulent sputum often containing clumps of eosinophils. A low-grade fever, a moderately enlarged spleen, an eosinophilia up to 88 per cent and a moderately accelerated sedimentation rate

A case of Loeffler's syndrome is presented. The eosinophilia was more marked than it has been in the majority of reported cases, and appeared to respond to treatment with Mapharsen. No definite etiologic agent was found.

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## SUMMARY



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case the agglutination reaction and a skin test for brucellosis were negative. Trichinosis, which may have respiratory abnormalities as a significant feature of the disease,<sup>22</sup> is rare in this locality, and could be excluded by the clinical course and negative skin test. Other tropical diseases characterized by blood eosinophilia were excluded by clinical and laboratory studies. Although trichuriasis may at times be associated with urticaria and a moderate eosinophilia, it is doubtful whether it was a significant etiologic factor. Recently, Weingarten<sup>23</sup> in India described what he believes to be a new clinical entity, manifested by severe, paroxysmal bronchitis and a high eosinophilia, in which arsenicals are a specific and quickly acting remedy. The disease is characterized by a paroxysmal cough, expiratory dyspnea and occasional attacks of bronchial asthma, with mucopurulent sputum often containing clumps of eosinophils. A low-grade fever, a moderately enlarged spleen, an eosinophilia up to 88 per cent and a moderately accelerated sedimentation rate

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## SUMMARY

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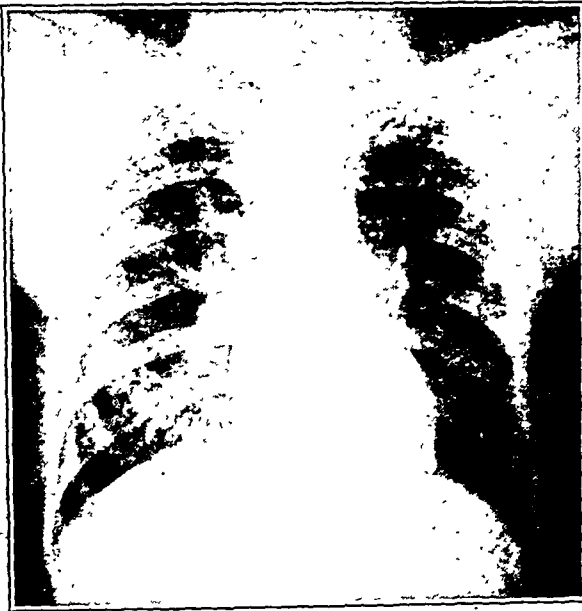


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are usually present. X-ray examination reveals disseminated mottling of both lungs, indicating small bronchopneumonic infiltrations. Although benign, this disease may last for several years. Arsenicals are specific, and the eosinophilia disappears rapidly after several injections. This was the basis for the treatment of our patient with Mapharsen.

The case reported appears to be typical of Loeffler syndrome in that the condition was benign; there was practically no elevation of temperature; the pulmonary infiltration shifted during the course of the disease, and a marked peripheral eosinophilia was present.

#### SUMMARY

A case of Loeffler's syndrome is presented. The eosinophilia was more marked than it has been in the majority of reported cases, and appeared to respond to treatment with Mapharsen. No definite etiologic agent was found.

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## MEDICAL PROGRESS

### THE PORPHYRINS\*

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BOSTON

THE average physician confronted with the subject of porphyrin metabolism pictures either a bewilderingly complex group of strange pigments obtained from stools and urine or an exceedingly rare disease characterized by sensitivity to light and acute abdominal pain. Actually, porphyrin derivatives are an essential part of the respiratory enzymes present in all living cells, and an understanding of their nature and relations may be expected to lead to improvement in the diagnosis and treatment of many human diseases. It is the purpose of this paper to discuss one of these porphyrins, protoporphyrin, and to indicate the role it plays in normal and abnormal human metabolism.

#### PROTOPORPHYRIN

The important chemical and physiologic roles of the substance protoporphyrin concern its integration into the iron-containing enzymes and pigments. Heme or hematinlike substances are formed when iron enters the center of the protoporphyrin ring, and the heme group combines with various specific proteins to form compounds such as blood hemoglobin, muscle hemoglobin, catalase, peroxidase and the cytochromes. These are essential and widely distributed substances in the body, and their specific physiologic or enzymatic functions are determined by the type of protein attached to the heme group. Although the heme group does not determine the specific function, it is nonetheless important as a common denominator of this whole group of substances. As compared with its appearance in these iron compounds, protoporphyrin free of iron and protein does not occur in large amounts in the body. It is present largely in the young cells of the red-cell series in the bone marrow and the peripheral blood.

Protoporphyrin was first found to be an iron-free derivative of hemoglobin by Kämmerer<sup>1</sup> in 1923. He demonstrated this by diluting blood with broth and inoculating it with fecal bacteria and putrid material from gangrenous lesions and bronchiectatic cavities, and incubating it for four to six days. Hoagland<sup>2</sup> had shown in 1917 that sterile autolysis of muscle resulted in a pigment identical with protoporphyrin, which by further hydrolysis changed

into hematoporphyrin. In 1924, the porphyrin present in natural hemin was crystallized and was shown by Fischer<sup>3</sup> to be protoporphyrin. Other studies followed.<sup>4-7</sup>

Protoporphyrin occurs in feces as a bacterial decomposition product of hemoglobin, and is chiefly exogenous.<sup>8-10</sup> Formation also takes place by bacterial decomposition of different types of tissue, such as the calf's heart and the liver, lung and uterus of various species.<sup>5</sup> Protoporphyrin 9 has been found in sheep liver by Rimington.<sup>11</sup> Excluding the above sites, the distribution of protoporphyrin in nature is somewhat bizarre. It is found in large amounts in the Harderian gland of the rat family.<sup>12</sup> It is apparently an excretion product of this gland, and none is produced for utilization in the animal. Protoporphyrin occurs as a pigment of the egg shells of certain birds, such as the plover, that nest in the open.<sup>13</sup> It has been found in incubated hens' eggs.<sup>14</sup> It is present in alkalized yeast, in plants such as peas, corn and beans and in the leaves of the ash and the maple.<sup>15-19</sup>

#### RELATION OF PROTOPORPHYRIN TO OTHER PORPHYRINS

Considerable knowledge of the structure and chemical properties of the various porphyrins exists, but the physiologic relations are rather obscure. All the porphyrin compounds consist of a basic porphyrin ring made up of four pyrrol groups attached to each other by methene linkages. The identity of a particular porphyrin is the result of the type and position of radicals attached to eight substitution points along the porphyrin ring. Porphyrin compounds in the body fall into two groups — first, those having four each of two different radicals in the eight substitution points along the porphyrin ring, and second, those having three radicals divided into four of one type and two each of the others. The first group has four possible isomers and the second has fifteen.

Examples of the first group are coproporphyrin and uroporphyrin. Both have four of two different types of radicals attached to the porphyrin ring. The four isomers that any porphyrin in this group may conform to are termed "types" and are numbered from 1 to 4. Only Types 1 and 3 are found

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infiltration. These findings were not transitory. Repeated examinations over a period of six months revealed no significant changes. Diffuse pulmonary infiltration, fever and eosinophilia have been reported in chronic brucellosis,<sup>21</sup> but in the present



FIGURE 3.

case the agglutination reaction and a skin test for brucellosis were negative. Trichinosis, which may have respiratory abnormalities as a significant feature of the disease,<sup>22</sup> is rare in this locality, and could be excluded by the clinical course and negative skin test.

Other tropical diseases characterized by blood eosinophilia were excluded by clinical and laboratory studies. Although trichuriasis may at times be associated with urticaria and a moderate eosinophilia, it is doubtful whether it was a significant etiologic factor. Recently, Weingarten<sup>23</sup> in India described what he believes to be a new clinical entity, manifested by severe, paroxysmal bronchitis and a high eosinophilia, in which arsenicals are a specific and quickly acting remedy. The disease is characterized by a paroxysmal cough, expiratory dyspnea and occasional attacks of bronchial asthma, with mucopurulent sputum often containing clumps of eosinophils. A low-grade fever, a moderately enlarged spleen, an eosinophilia up to 88 per cent and a moderately accelerated sedimentation rate

are usually present. X-ray examination reveals disseminated mottling of both lungs, indicating small bronchopneumonic infiltrations. Although benign, this disease may last for several years. Arsenicals are specific, and the eosinophilia disappears rapidly after several injections. This paper was the basis for the treatment of our patient with Mapharsen.

The case reported appears to be typical of the Loeffler syndrome in that the condition was benign; there was practically no elevation of temperature; the pulmonary infiltration shifted during the course of the disease, and a marked peripheral eosinophilia was present.

#### SUMMARY

A case of Loeffler's syndrome is presented. The eosinophilia was more marked than it has been in the majority of reported cases, and appeared to respond to treatment with Mapharsen. No definite etiologic agent was found.

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Porphyrins of the second group are characterized by three different radicals substituted and fifteen isomers; in this group are included deuteroporphyrin,

of the porphyrins should be discussed. The first concept is a phenomenon described by Fischer and Orth<sup>20</sup> and called by them "the dualism of the porphyrins." By this is meant the constant appearance in the body of two isomer types as the result of current independent synthesis. It is considered im-

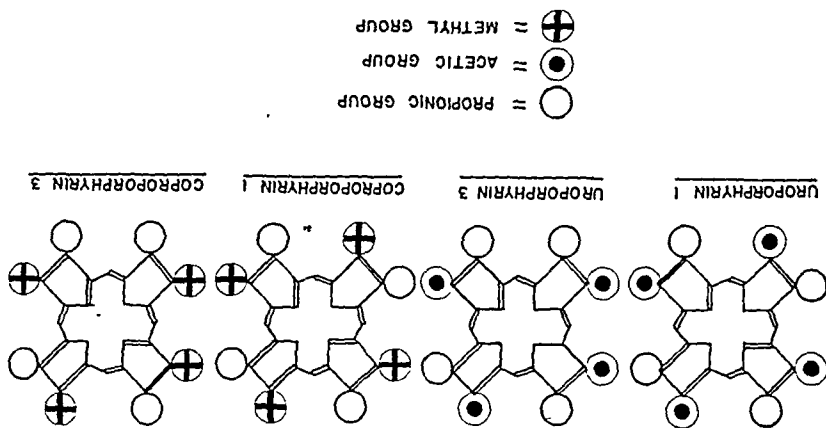


Figure 1.

possible for the two types to merge or interchange unless there is a breaking up of the stable porphyrin ring and a resynthesis. This is extremely unlikely. Thus, a Type 1 porphyrin may be formed from, or changed into, other Type 1 compounds, but it is impossible for either type to change into the other. When there is found in the organism a highly specialized porphyrin such as protoporphyrin 9, a Type 3

The uroporphyrins and coproporphyrins are more carboxylated than protoporphyrin or the other more complex porphyrins. If the two vinyl groups of

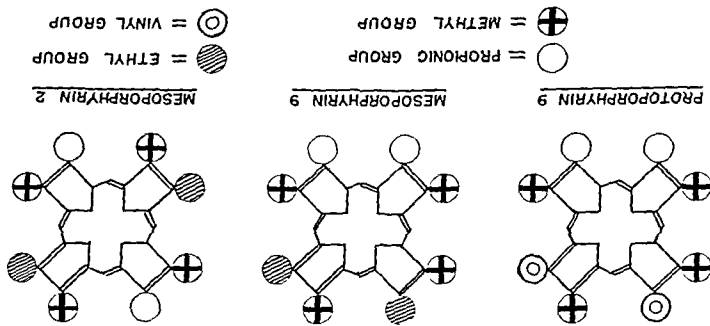


Figure 2.

protoporphyrin are saturated and a carboxyl group is added, it is transformed into coproporphyrin. If, further, coproporphyrin has the four methyl groups altered and carboxylated to acetic groups, a transformation arises whether such a carboxylation occurs in the body and whether the simpler porphyrins are excretion products of protoporphyrin.

Before an attempt is made to answer this question, certain important concepts concerning the relations of "enzymatic control," partial credit for which should be given to Dobriner,<sup>22</sup> Rimington has hypothesized that a ratio exists between the Type 3

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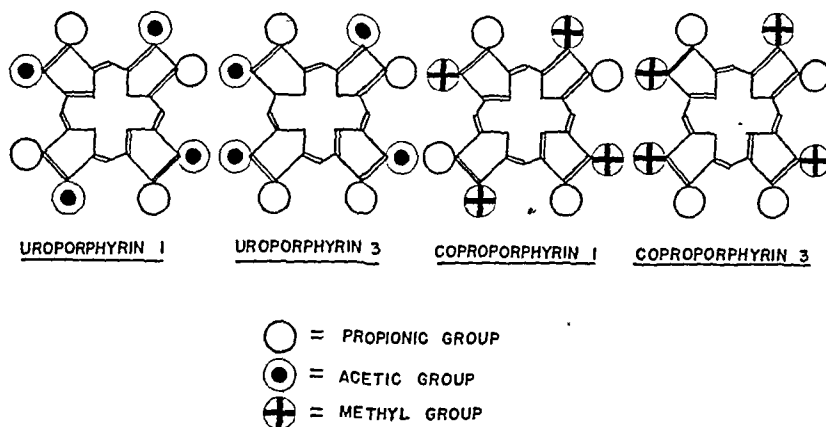


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mesoporphyrin, hematoporphyrin and protoporphyrin. Each of the fifteen isomers conforms to one of the four types in the first group of simpler porphyrins. Examples of these compounds are shown in Figure 2.

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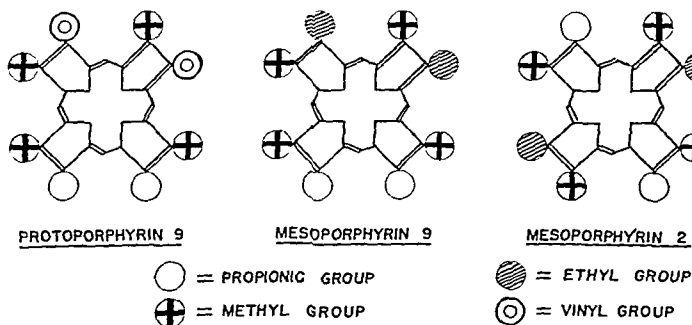


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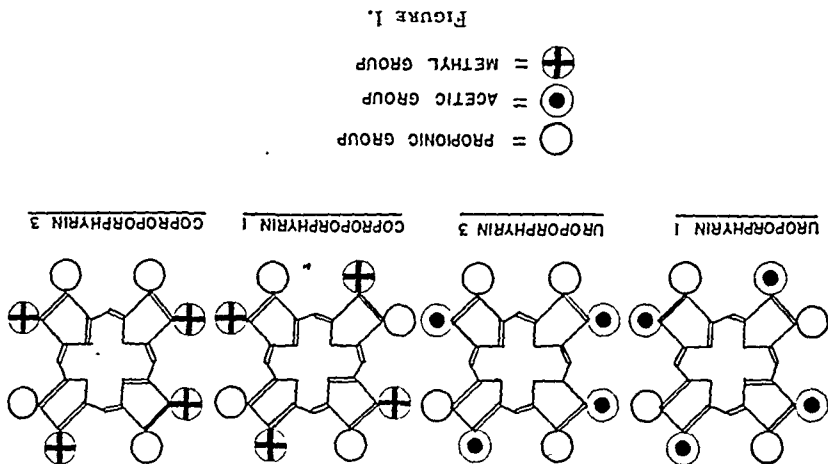
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A second concept consists of Rimington's<sup>21</sup> theory of "enzymatic control," partial credit for which should be given to Dobriner.<sup>22</sup> Rimington has hypothesized that a ratio exists between the Type 3

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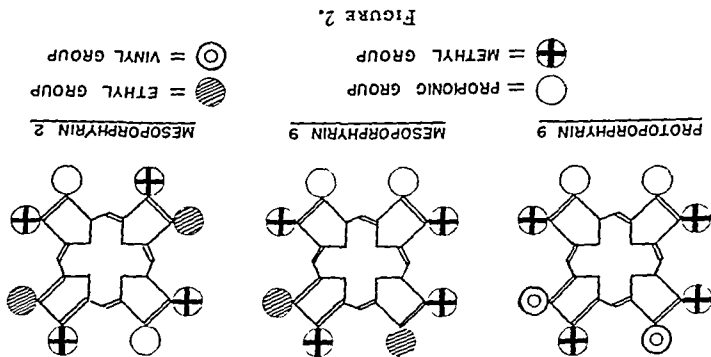
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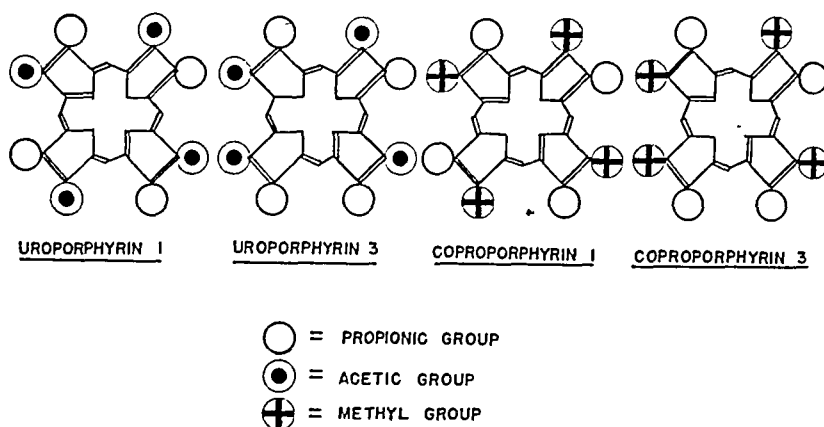


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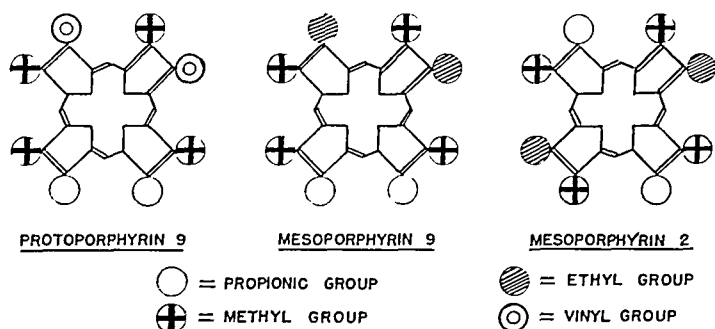


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and the Type 1 series of porphyrin compounds in the body, this ratio being greatly in favor of the former. The explanation lies in the hypothetical formation of porphyrins from two dissimilar dipyrromethenes. — each one half a porphyrin ring with suitable radicals attached, — which may be designated as X and Y. The radicals of the dipyrromethenes are arranged so that when X and Y unite a porphyrin such as protoporphyrin 9 (Type 3) is formed. This reaction is controlled by enzymes, but a small fraction of X molecules combine with other X molecules to form a Type 1 porphyrin. It would be reasonable to expect that a small fraction of dipyrromethene Y molecules would combine with each other to form a Type 2 porphyrin, but

uroporphyrin and their isomers occur in the body if mesoporphyrin<sup>23,24</sup> and deuteroporphyrin<sup>25-27</sup> are excluded as exogenous in the feces. Vigorous investigation of uroporphyrin and coproporphyrin has revealed few generalizations. Uroporphyrin and coproporphyrin are found largely in the urine and feces.<sup>23</sup> Coproporphyrin is considered the only porphyrin normally present in urine.<sup>29,30</sup> Some authorities<sup>31</sup> report that normal bile contains coproporphyrin I, and other investigators<sup>32</sup> find no coproporphyrin in bile. When an increase of uroporphyrin or coproporphyrin occurs in disease, the normal liver causes Type 1 porphyrins to be excreted in both the urine and the bile, but Type 3 isomers of these substances are excreted exclusively in the urine.<sup>25</sup> Copropor-

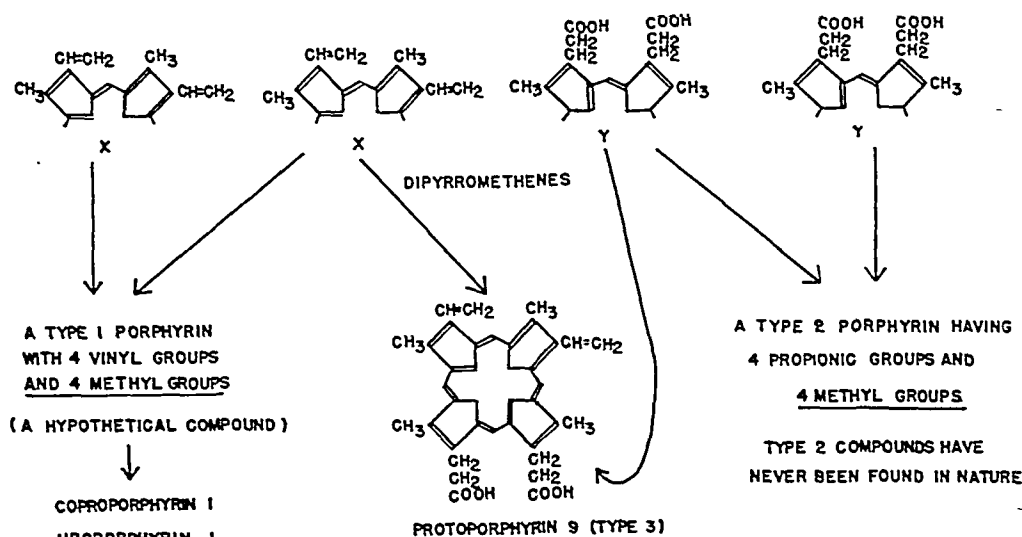


FIGURE 3.

none of this has ever been found in nature or the body. This discrepancy has been anticipated by postulating that the only leak in the reaction centers around the combination of similar X molecules, the enzyme system entirely preventing the combining of Y molecules. The whole reaction is theoretically tenable and can be expressed structurally as shown in Figure 3. These theories furnish a convenient explanation for the presence of uroporphyrin and coproporphyrin I in the body as breakdown products either of Type 1 protoporphyrin or of some other as yet undiscovered complex Type 1 porphyrin. Another theory presupposes that uroporphyrin 3 and coproporphyrin 3 are formed directly from dipyrromethenes and that the Type 1 analogues occur as an artefact of their synthesis.

The occurrence of porphyrins in the diseased and normal body should be briefly summarized in a search for facts correlating with these theories. Besides protoporphyrin only coproporphyrin and

pyrin excretion in the urine and the urinary fecal ratio have been thought to be sensitive tests of hepatic function,<sup>28</sup> but this is not so.<sup>33</sup>

In diseases characterized by marked increases of uroporphyrin and coproporphyrin there has never been found any abnormality of the protoporphyrin metabolism. Such diseases are known as porphyria if they are due to inborn errors of metabolism or as porphyrinuria if secondary to other diseases. Congenital porphyria has the clinical features of photosensitivity, red teeth and bones and dark-red or brown urine.<sup>34</sup> Uroporphyrin 1 and 3 are deposited in the skeleton, and Type 1 isomers of uroporphyrin and coproporphyrin are found in large amounts in the urine. Acute porphyria is associated with acute episodes of abdominal cramps, neurogenic paralyses and mental symptoms, and also with dark urine.<sup>35</sup> The urine contains large amounts of Type 3 uroporphyrin and coproporphyrin. No involvement of protoporphyrin has been found to occur in these

diseases, and there are present no marked anemias that might be attributed to an error in the formation of protoporphyrin. Applying the theory of enzymatic control to congenital porphyria, the increases of Type 1 porphyrins could be interpreted as a lack of the normal retardation of these compounds, resulting in an abnormal ratio between the Type 1 and Type 3 porphyrins. No protoporphyrin I has ever been reported in patients with this disease.

The porphyrinurias are diseases in which the excess of porphyrin is usually coproporphyrin of either type secondary to other disease, such as liver disease,<sup>36</sup> pellagra,<sup>37</sup> febrile conditions<sup>38</sup> and diseases of the blood-forming organs. Protoporphyrin has never been involved, except in diseases in which anemia exists, which will be treated under a separate heading.

It has been assumed by most authors that Type 3 coproporphyrin and uroporphyrin may well be excretion products of a more complex, specialized porphyrin compound such as protoporphyrin. Schumm<sup>39</sup> in 1923 found no coproporphyrin in the urine of patients on a meat-free diet and was able to demonstrate its appearance following feeding with hemoglobin and blood sausage. In 1926, he<sup>40</sup> found increased coproporphyrin in the feces following similar feedings. Van den Bergh et al.<sup>41</sup> attempted to prove that the liver changes protoporphyrin to coproporphyrin by perfusing livers with protoporphyrin solutions and demonstrating coproporphyrin in the bile in increased amounts. The isomer of protoporphyrin was not identified. Vigliani and Sonzini<sup>42</sup> in a similar experiment found no coproporphyrin and most of the protoporphyrin that was administered present in the bile in a patient with a complete external biliary fistula. By far the most conclusive investigations on this subject were those of Watson, Pass and Schwartz,<sup>43</sup> who repeated and modified van den Bergh's experiments. Only increases of Type 1 coproporphyrin were demonstrable, and these increases, although distinct, were small and represented only a fraction of the administered protoporphyrin. It is impossible for coproporphyrin 1 to be a direct product of protoporphyrin 9, so that to explain the increase of the latter it must be hypothesized that protoporphyrin stimulates synthesis of coproporphyrin 1 in some unknown fashion.

The hypothesis of so-called "dualism of the porphyrins" would be immeasurably strengthened if it could be demonstrated that small amounts of a Type 1 protoporphyrin are present in hemoglobin along with the usual Type 3 protoporphyrin. This would establish a highly specialized functioning end product of the Type 1 series of porphyrins and afford a substance from which coproporphyrin and uroporphyrin 1 could be reasonably derived. When Fischer<sup>43</sup> in 1939 described experiments identifying a small fraction of natural hemoglobin as containing protoporphyrin 2, a Type 2 compound, wide inter-

est was aroused and the matter was considered as solved. His experiments depended on the transformation of protoporphyrin to mesoporphyrin, with esterification and identification of the latter. However, in a second, obscurely titled paper, Fischer and Schroder<sup>44</sup> retracted the earlier findings on the identification of mesoporphyrin 2 (Type 1) as a derivative of the hemoglobin of normal blood. Conversions of the supposed mesoporphyrin 2 to rhodins and verdins showed no trace of mesorhodin 2 or mesoverdin 2. The conclusions of these workers were that no protohemin 2 (Type 1) exists in normal blood.

These facts change considerably the attitude toward the Type 1 porphyrins, uroporphyrin and coproporphyrin. There are no other Type 1 porphyrin compounds known in the body from which they might be derived or into which they might change. There is no evidence at present that they are anything more than abortive side products of porphyrin synthesis. Relegating them to an abortive state does not by any means invalidate the theory of dualism of the porphyrins or that of enzymatic control. The term "abortive" in this sense refers to structural evolution and function, and not to quantity or pathologic significance.

Certain miscellaneous aspects of the relations of protoporphyrin to the other porphyrins must be mentioned. Properties of photosensitization common to several of the porphyrins have not been found to be shared with protoporphyrin.<sup>28</sup> It is never deposited in the bones, as is uroporphyrin.<sup>45</sup> Porphyrins of several types have been known to combine with proteins such as fibrinogen, albumin and globin.<sup>46,47</sup> Light hydrolyzes the proteins in the presence of porphyrin and oxygen. Fischer<sup>48</sup> has suggested a correlation of the toxicity of the porphyrins with the number of carboxyl groups present in each. The order of toxicity as judged by the production of light shock in mice is as follows: hematoporphyrin 9, Type 1 uroporphyrin, deutero-porphyrin 9, Type 1 coproporphyrin and protoporphyrin 9; Type 3 coproporphyrin is only slightly toxic, and uroporphyrin 3 is nontoxic.<sup>28</sup>

#### PRECURSORS OF PROTOPORPHYRIN

The steps in the formation of protoporphyrin *in vivo* are unknown. In 1929, Fischer<sup>49,50</sup> synthesized heme from simple pyrrols. Dipyrromethenes were formed from pyrrols and then condensed to a Type 3 porphyrin that in a series of steps became protoporphyrin 9. In the body Fischer<sup>20</sup> has suggested simpler sources, such as proline, oxyproline and tryptophane. Dipyrromethenes probably form a step in the synthesis. There are two clues to the presence of dipyrromethenes in the body—the pentdyopent reaction and the porphobilinogen test. In neither of these reactions has a dipyrromethene been shown to exist free inside the body. The pentdyopent reaction consists of a spectroscopic

absorption band appearing at 525 millimicrons when hemoglobin, heme, bilirubin or urobilin solutions are treated with hydrogen peroxide, particularly in alkaline solution in the presence of sodium hydrosulfite.<sup>20</sup> Fischer and Stern<sup>31</sup> have identified the substance producing the absorption band as a dipyrromethene. The relation of protoporphyrin to the pentdyopent reaction is mentioned only twice in the literature. Hulst and Grotepass<sup>52</sup> state that pentdyopent may be prepared from protoporphyrin, although the oxidative process is much slower. Fischer and Müller<sup>53</sup> report that none of the porphyrin compounds, including protoporphyrin, give the pentdyopent reaction. The porphyrin ring can be readily broken down to the dipyrromethenes found in the pentdyopent reaction if iron and globin are attached or if it has already been broken down to a straight chain of four pyrrol groups, as in bilirubin or urobilin.

Porphobilinogen was first noted in the urine as the substance in porphyria that gave a positive Ehrlich reaction not due to urobilinogen. It was discovered by Waldenström<sup>54</sup> in 1937. It is considered to be a dipyrromethene, and a simple test for it has been devised and the literature reviewed by Watson.<sup>55</sup>

#### BREAKDOWN OF THE PROTOPORPHYRIN RING

This subject is intimately tied up with the breakdown of hemoglobin and the iron enzymes. The probability of breakdown through uroporphyrin and coproporphyrin has already been discussed. The vast majority of protoporphyrin in hemoglobin is broken down and eliminated as bile pigments, and degradation to porphyrins is minimal. Iron does not separate from the heme until the porphyrin ring has been split open,<sup>56,57</sup> thus avoiding a free porphyrin stage.

In 1935, Schreus and Carrié<sup>58</sup> reported the formation of protoporphyrin by the action of ground-up liver on hemoglobin at 36 to 60° C. They believed that the effect was due to an enzyme that they called "hemase," and considered the formation of protoporphyrin intermediate in the breakdown of hemoglobin to bile. When the reaction was alkaline, bile formed, but this occurred at a higher maximum temperature, attributed by them to the possible destruction of catalase. These findings have never been confirmed, but if true are of great importance. Evidence militates against such a process predominating *in vivo* because of Lemberg's<sup>56</sup> demonstration that in hemoglobin the porphyrin ring is split open prior to the departure of the iron.

#### RED CELLS AND HEMOGLOBIN

Protoporphyrin was first found in red cells by van den Bergh and Hyman<sup>59</sup> in 1928. Grotepass<sup>60</sup> isolated it and identified it as a Type 3 porphyrin. The association of protoporphyrin and reticulocytes was noted by two different groups. Watson and

Clarke<sup>61</sup> ingeniously showed that most of the protoporphyrin is contained in the reticulocyte-rich stratum of centrifuged cells. They were also able to show that protoporphyrin is mutually precipitable with certain stains, such as cresyl blue, that stain reticulocytes. The precipitated protoporphyrin-dye substance microscopically resembles the framework of reticulin in reticulocytes, but the precipitation phenomenon is probably due to a buffering effect and not to the formation of an actual compound between the protoporphyrin and the dye.<sup>62</sup> De Langen and Grotepass<sup>63</sup> arrived at similar conclusions concerning the large amount of protoporphyrin in reticulocytes. Seggel<sup>64,65</sup> presents evidence that the erythrocyte protoporphyrin resides in cells called "fluorescytes," which can be identified only by their fluorescence in ultraviolet light. These cells normally occur in largest numbers in the bone marrow, their appearance and increase in the peripheral blood being associated with conditions causing reticulocytosis. Seggel has pointed out that fluorescytes appear later and decline more slowly than do reticulocytes in cases of pernicious anemia under liver treatment. Watson's<sup>62</sup> latest studies reveal a discrepancy between erythrocyte protoporphyrin levels and reticulocyte percentages in treated cases of pernicious anemia. This casts some doubt on whether all reticulocytes contain large amounts of protoporphyrin. To explain this discrepancy Watson has mentioned the possibility that in the peak of the reticulocyte response following liver therapy in pernicious anemia there may be a large number of reticulocytes that have had a megaloblastic origin and do not contain much protoporphyrin. Incubation of red cells for twenty-four to forty-eight hours resulted in a decrease of the reticulocytes but an increase of protoporphyrin. When experimental phenylhydrazine anemia was produced in rabbits, the protoporphyrin in red cells more nearly paralleled the reticulocytes than in pernicious anemia. Reticulocytes derived from megaloblasts would presumably not be present in the phenylhydrazine anemia.

The status of protoporphyrin in the bone marrow is not entirely clear. Borst and Königsdorffer<sup>66</sup> found it in normal marrow and increased in certain conditions, notably pernicious anemia. It was contained largely in erythroblasts and megaloblasts and occurred in the megaloblasts in pernicious anemia. It is generally conceded that the bone marrow contains large amounts of protoporphyrin in pernicious anemia,<sup>32,58</sup> but there is a difference of opinion about its presence in megaloblasts. Seggel and his co-workers were unable to find it there before or after treatment. Stasney and McCord<sup>67</sup> found protoporphyrin in megaloblastic marrow, but the amount increased as the marrow became normoblastic.

Lead poisoning has been found by Vigliani and his co-workers<sup>68,69</sup> to give rise to high protoporphyrin



levels in the red cells and plasma. This disease has long been associated with increased amounts of coproporphyrin 3 in the urine. In most diseases showing hyperactive erythropoiesis it is coproporphyrin 1 that is found in abnormal amounts. This finding is so regular that the presence of coproporphyrin 1 in the urine is said to be an index of increased erythropoiesis. In pernicious anemia coproporphyrin 1 has been found increased in the urine and plasma in relapse.<sup>31,32</sup> Rimington<sup>70</sup> has shown that coproporphyrin 3 predominates in the urine following sulfanilamide treatment. Both Rimington and Watson<sup>71</sup> have hypothesized that lead and sulfanilamide may interfere with the introduction of iron into the porphyrin molecule, resulting in the formation and excretion of coproporphyrin 3. Very few other investigations of protoporphyrin in diseases of the blood have been made except for Watson's<sup>62</sup> preliminary studies employing the photoelectric method, which showed moderately elevated levels in several diseases associated with reticulocytosis.

Peripheral red-cell protoporphyrin should probably be considered as a supply of one of the building blocks of hemoglobin. Increased supplies in the peripheral blood occur in conditions characterized by rapid formation of red cells in the marrow and the premature throwing off of some forms of young red cells into the circulation. The factors governing the release of these cells from the bone marrow apparently regulate the peripheral blood-protoporphyrin level. Such factors include the pathogenesis of the particular anemia, depletion of the peripheral red cells and the ability of the bone marrow to regenerate young forms. Increased protoporphyrin levels are probably secondary to these conditions. The temptation must be resisted to consider that in pernicious anemia there is an arrest of protoporphyrin synthesis, with resumption of this synthesis manifested by the increased protoporphyrin following the administration of liver extract.

#### PROTOPORPHYRIN IN URINE

In kidneys perfused with various porphyrins, Grotepass and Hulst<sup>72</sup> reported that uroporphyrin was excreted rapidly by the kidney, coproporphyrin less so, and protoporphyrin not at all. In spite of the vast quantity of research done on urinary porphyrins, there has been only one report of protoporphyrin in the urine. Boas<sup>73</sup> in 1933 reported finding protoporphyrin in the urine of diabetic patients with jaundice, cholelithiasis, carcinoma of the gall bladder and other conditions. He used the ordinary ether-acetic and hydrochloric acid extraction methods. All other observers are in complete agreement that protoporphyrin has never been found in urine. No protoporphyrin has ever been reported in the hemoglobinurias or myoglobinurias or following the breakdown of red cells in the urine, as in hematuria.

#### PROTOPORPHYRIN IN ENZYMES

Fischer and Orth<sup>20</sup> have reviewed the early work on the identification of Type 3 porphyrins in enzymes and pigments. The more recent studies have been covered by Sumner and Somers.<sup>74</sup> The porphyrin in myoglobin was identified by Schönheimer<sup>75</sup> in 1929 as protoporphyrin. In spirographis hemin the porphyrin present is Type 3 protoporphyrin.<sup>12</sup>

Although not an oxidase, catalase is classified with the oxidases because of its structural similarity to them and because of its close connection to physiologic oxidation. It occurs in all forms of life except a few micro-organisms, and its action consists of protecting living things from hydrogen peroxide. Zeile and Hellström<sup>76</sup> showed that catalase is a hematin compound. Later, Stern<sup>77</sup> demonstrated that the hematin of catalase is protohematin 9. The highest concentrations are in the erythrocytes and liver.

Another important enzyme, peroxidase, occurs in all plant cells, although its occurrence in animals is problematical. It catalyzes the oxidation of large numbers of phenols and amines in the presence of hydrogen peroxide. Theorell<sup>78</sup> demonstrated it to be a hematin-protein compound. Verdoperoxidase, so called because of its color in the dry state, has a similar action and occurs to the extent of 1 per cent in white blood cells.<sup>74</sup> It contains 0.1 per cent iron and is assumed to be a heme-protein compound.

Cytochrome is widely distributed in nature and in the body. The bulk of investigation has been on cytochrome C because Types A and B are extremely labile. Cytochromes probably function as carriers of electrons and thus participate in complicated reactions leading to the removal of hydrogen from metabolites and the formation of water. Cytochrome C is a hematin-protein compound whose heme group differs from protoheme in having a tertiary-ring base condensed around it. It is bound to protein by two histidine-imidazole groups attached to iron on either side of the flat hematin disk and by thioether bindings to the ethyl groups (the ethyl groups taking the place of the usual vinyl radicals).<sup>79,80</sup> These bindings to the protein explain why cytochrome is not auto-oxidizable, since oxygen cannot approach the iron; for the same reason, cytochrome cannot unite with carbon monoxide or cyanide at ordinary pH values.

The isomer of protoporphyrin has not been identified in the case of all the iron enzymes. No such exhaustive study has been made on any of the enzymes as that by which Fischer excluded the presence of protoporphyrin 2 (Type 1) in blood. In the review of these compounds it can be seen that protoporphyrin and iron appear to be inseparable in any physiologic role, and that they are combined with a protein. A generalization can probably be made that neither protoporphyrin alone nor iron occurring alone, as in hemosiderin,<sup>81</sup> have any useful function or physiologic role.

### MISCELLANEOUS STUDIES CONCERNING PROTOPORPHYRIN

According to Hinsberg and Rodewald,<sup>82</sup> administration of protoporphyrin and hematoporphyrin to various animals resulted in an increased melanophore-distributing hormone of the hypophysis. The injected animals formed a substance inactivating this hormone, and the authors associate this inactivating agent with the serum of cancer cases. Hinsberg<sup>83</sup> also reported premature follicle formation in the ovaries of mice following injection of protoporphyrin and hematoporphyrin.

### CHEMICAL ASPECTS OF PROTOPORPHYRIN

Fischer and Orth<sup>20</sup> have described the physical and chemical properties of protoporphyrin. It has been crystallized in two forms, and the crystals are usually yellow to reddish. It is soluble in chloroform, pyridine and ether, in acetic and hydrochloric acids and in aqueous solutions of alkalis. It is reddish in solution, like the other porphyrins. All the porphyrins produce intense absorption bands in the visible spectrum. The number and position of the bands vary with the pH, the temperature and the solvent, but under standard conditions the bands are characteristic for a given compound, all isomers having the same bands. A listing of the differentiating absorption bands of the porphyrins cannot be found in the English literature. Table 1 is modified from Vannotti.<sup>38</sup>

Protoporphyrin is differentiated from the other porphyrins by its spectroscopic bands, by the melt-

The fifteen isomers of protoporphyrin have not yet been separately synthesized, but Fischer and Orth<sup>20</sup> have synthesized twelve of the fifteen isomers of mesoporphyrin. Protoporphyrin and its methyl ester are unstable, particularly in the presence of light, and for isomeric or quantitative determinations it is customary to convert the protoporphyrin to mesoporphyrin and form the methyl ester of the latter. The esters of all the porphyrins crystallize more easily than do the porphyrins themselves, and the ester melting point is more distinct. Watson<sup>84</sup> has recently summarized the methods of conversion of protoporphyrin to its methyl ester, and has added an improved micromethod involving the reduction of hydriodic acid, acetic acid and ascorbic acid.

Protoporphyrin can be prepared in many different ways,<sup>1,2,85</sup> but the most convenient method is that of Fischer and Pützer,<sup>86</sup> whose description of it has never been translated into English. This method is as follows:

Six grams of hemin are heated to boiling with 300 gm. of formic acid of specific gravity 1.22. Six portions of 1 gm. each of finely powdered iron (specifically, "Kahlbaum for analysis") are introduced at five-minute intervals into the boiling liquid and boiled for fifteen more minutes after the last has been added. To avoid bumping it is necessary to shake the apparatus in a machine. After the total time reaction of forty minutes the entire hemin is transformed into porphyrin. It is then cooled off and filtered from the iron and the formed ferroformate. Protoporphyrin is precipitated by diluting with two to three volumes of water and adding solid ammonium acetate. The precipitate is freely washed with water and dried. In the filtrate there remains a small amount of protoporphyrin and much iron.

Grinstein and Watson<sup>87</sup> have recently reviewed the methods of purification of the crude product and have

TABLE 1. *Absorption Bands of Porphyrins in Various Solvents.*

PORPHYRIN	SOLVENT	ABSORPTION BANDS									
Protoporphyrin	Hydrochloric acid (25 per cent)*	602.4	582.2	557.2							
	Hydrochloric acid (25 per cent)†	602.7		557.2	410.8						
	Potassium hydroxide (N/10)*	645.2	591.0	539.7							
	Potassium hydroxide (N/10)†	642.0	591.0	540.0							
	Ether*	632.3	585.1	575.8	536.8	501.9					
	Chloroform†	630.6		575.3	540.7	506.9					
Protoporphyrin dimethyl ester	Pyridine†	632.8		576.0	541.0	507.0					
	Hydrochloric acid (25 per cent)*	668.8	603.4	583.4	557.0						
	Chloroform*	631.6	603.9	581.1	541.3	506.0					
Hematoporphyrin	Hydrochloric acid (25 per cent)*	595.8	575.5	551.7	527.9	510.5					
	Hydrochloric acid (25 per cent)*	593.1	572.4	548.7	524.8	508.7					
	Ether*	623.3	612.4	596.6	578.3	567.6					
Mesoporphyrin	Chloroform†	621.0			565.9	559.0	528.6	494.6			
	Hydrochloric acid (25 per cent)*	593.6		550.2			552.8	498.2			
	Hydrochloric acid (25 per cent)*	593.6	574.6	550.9	405.8						
Coproporphyrin	Ether†	623.6	568.4	526.3	495.0						
	Pyridine†	622.5	567.5	531.5	499.5						
	Hydrochloric acid (25 per cent)*	596.6	577.6	553.6	511.3						
Uroporphyrin	Hydrochloric acid (25 per cent)†	597.1		554.1	410.7						
Deuteroporphyrin	Hydrochloric acid (25 per cent)*		591.5	548.5							
	Hydrochloric acid (25 per cent)*		589.5	569.0	546.6						
	Hydrochloric acid (5 per cent)*		595.7	576.8	566.8	525.9	494.1	430			
	Ether*	621.7									

\*According to Fischer.

†According to Schumm.

ing points of its methyl esters, by its solubility in sodium hydroxide and by its hydrochloric acid number. The hydrochloric acid number is the concentration in percentage of hydrochloric acid that, when shaken with equal parts of ether, removes two thirds of the porphyrin from the ether. Dobriner<sup>28</sup> gives a table of these constants that is taken from Fischer and Orth.<sup>20</sup>

modified Hamsid's method. The protoporphyrin is dissolved in a small amount of chloroform, and petroleum ether is added until a precipitate begins to form; crystallization is completed in an icebox. Further purification occurs on forming the dimethyl ester, and Watson<sup>87</sup> has devised a method of purification of the ester using chromatography and eluting a chloroform-dissolved ester with

petroleum ether.<sup>87</sup> A method of transformation of protoporphyrin to protohemin is described by Fischer and Pützer<sup>86</sup> in which ferrous acetate or ferric chloride is allowed to combine with protoporphyrin, depending on whether divalent or trivalent iron is to be added.

Grinstein and Watson<sup>88</sup> review the older methods of extraction of free protoporphyrin from blood cells and present a new modification. Previous methods used spectroscopic or fluorometric determinations of the protoporphyrin. Watson's method employs the photoelectric colorimeter's measurement of the absorption of light at 400 millimicrons, the maximum absorption band of protoporphyrin being at 407 millimicrons. It has the advantages over any one of the older methods of simplicity and accuracy. It has much wider possibilities for clinical investigative studies than do the other methods. In brief, the primary extraction is made with a mixture of glacial acetic acid and ethyl acetate, followed by successive extractions with hydrochloric acid, ether and again hydrochloric acid. Values are expressed in gamma per 100 cc. of erythrocytes, normal values ranging from 20 to 45. In disease, protoporphyrin may be elevated to 200 and even 430 gamma.<sup>62</sup>

Extraction of other organs and tissues usually depends on acetic acid-ether extracts of the ground tissues, purification being done by a series of extractions involving hydrochloric acid and ether. Neutralization of the hydrochloric acid solution with acetate, using Congo red as an indicator, drives the porphyrin back into the ether. Hydrochloric acid solutions of over 5 per cent always extract the porphyrin from the ether. The protoporphyrin in liver has been extracted in this manner by Fischer<sup>89</sup> and by Rimington.<sup>11</sup>

#### SUMMARY

It may be said that protoporphyrin is intimately associated with certain of the pigments and enzymes concerned in oxidative processes. Iron and protoporphyrin have always been found in combination in physiologic conditions. Neither has been proved to have any important separate functional capacity. The protoporphyrin forms a convenient and suitable binding necessary to the iron.

Circumstantial evidence points to coproporphyrin 3 and uroporphyrin 3 as excretory products of protoporphyrin. Coproporphyrin 1 and uroporphyrin 1 cannot be breakdown products of protoporphyrin 9, the only protoporphyrin known in the body. If in the future a Type 1 porphyrin is found in a pigment or enzyme, uroporphyrin 1 and coproporphyrin 1 will be acceptable as its possible excretion products. In the meantime they must be considered as abortive side products of porphyrin synthesis.

Protoporphyrin is found free in red cells, and is associated with certain young cells called "fluorescytes" and with reticulocytes. In diseases in

which these cells are numerous, the red-cell protoporphyrin increases and can be considered a supply for the building up of hemoglobin. Many recent advances have been made relating to qualitative and quantitative determinations. Clinical investigation of the protoporphyrin of blood in disease has been facilitated.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31011

#### PRESENTATION OF CASE

*First admission.* A fifty-five-year-old woman was admitted to the hospital with an impacted fracture of the neck of the right femur.

About twenty-four hours before admission the patient became dizzy and fell to the floor. An x-ray examination revealed an incomplete impacted fracture of the right femoral neck. Four years previously the patient had fallen at home and incurred a similar fracture of the left femoral neck, which was treated by traction with a good result. One and a half years prior to admission she had fallen on her left shoulder with a resultant impacted fracture of the surgical neck of the left humerus which also healed with a good result. At about that time she had had an attack of "nervous prostration" lasting six weeks, with frequent "dizzy" or "sinking" spells, which caused her to fall down. About two months before entry she had fallen and twisted her ankle. The patient was said to have had congenital syphilis; this was diagnosed at the age of three years and apparently was inadequately treated. Her teeth had been poor and were extracted at an early age. She had two adult children by her first husband; both were born after a full-term normal pregnancy and both had negative Hinton tests. She had been married to her second husband for two and a half years.

Physical examination on admission revealed a fairly well-developed and well-nourished woman incessantly picking at the bedclothes or rubbing her hands together; she was vague about her past history and unco-operative. There was spasm about the right hip and limitation of motion but no shortening.

The temperature was 99°F., the pulse 86, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

Examination of the blood showed a red-cell count of 4,010,000, with 75 per cent hemoglobin, and a white-cell count of 6800. The urine varied in specific gravity from 1.002 to 1.014, with a 0 to a +++ test for albumin and a sediment containing few to many white cells and a few red cells. The blood protein, calcium, phosphorus and phosphatase levels were

normal. Blood Hinton and Wassermann tests were positive.

Since the fracture was impacted and in good position, it was treated with balance suspension. The patient throughout her stay was unco-operative, suspicious and difficult to manage. A psychiatric examination showed her to be emotionally unstable — "irritable and belligerent, but not demented or psychotic"; there was no confusion or impairment of memory. At the end of six weeks the patient resisted efforts to get her up on crutches, and she was discharged against advice.

*Second admission* (four months later). Following her discharge the patient was able to get about a little, but her activity was limited by the frequent occurrence of "sinking" spells, during which she became weak and was forced to sit down for a time. Six hours before entry, her husband left her feeling quite well. Half an hour before entry he returned and found her in her chair, comatose and stiff.

Physical examination revealed a comatose woman breathing in gasps. The only response was slight withdrawal of the extremities from painful stimuli. All the extremities were spastic. The head and eyes were turned to the left. There were spontaneous, horizontal, nystagmoid movements. The pupils did not react to light. There was no papilledema. All the deep tendon reflexes were brisk, particularly on the left. There were bilateral extensor plantar responses, and a positive Hoffmann sign on the left.

A lumbar puncture revealed clear fluid under a pressure equivalent to 130 mm. of water and containing 6 lymphocytes and 15 red cells per cubic millimeter. The total protein was 234 mg. per 100 cc. The Wassermann test was positive. The gold-sol curve was 555555500. The urine had a specific gravity of 1.022, with no albumin or sugar but with a ++ test for acetone and a rare granular cast in the sediment.

The temperature on admission was normal, but four hours later it spiked to 105°F. and during the next twenty-four hours it rose to 108°F. The pulse rose to 160 and the respirations to 50.

The white-cell count was 16,100, with 80 per cent neutrophils. A blood culture was negative. A roentgenogram of the chest taken at the onset revealed indefinite fine areas of increased density in the left lung field. X-ray examination of the skull was negative. Sulfadiazine was administered (1.0 gm. every six hours) by Levine tube, and food and fluid intake were maintained in the same fashion. A second lumbar puncture revealed a cell count of 29 lymphocytes, 7 neutrophils and 29 red cells.

After reaching 108°F. on the third hospital day, the temperature gradually fell toward normal. The patient remained comatose. Deviation of the head and eyes to the left occurred intermittently. At times there was skew deviation of the eyes. On one occasion the pupils were reported to react slightly to light. The extremities were sometimes spastic and

\*On leave of absence.

sometimes flaccid. At times the tendon reflexes could not be obtained.

On the fourth hospital day, the temperature rose to 101°F., the lungs filled with coarse moist rales and the patient died.

### DIFFERENTIAL DIAGNOSIS

DR. RAYMOND ADAMS\*: Let us scrutinize this record with the purpose in mind of selecting data that point to the site of the pathologic process, leaving the matter of etiology until later.

In the early part of the history the outstanding symptoms were attacks of dizziness and sinking spells. In such attacks the patient had fallen repeatedly and had suffered numerous injuries. The first problem that confronts us, then, is the nature of these spells. Were they attacks of giddiness such as occur so often in nervous, anxious individuals, or were they attacks of vertigo such as are often observed in diseases of the labyrinth, eighth nerve or vestibular nuclei? Were they straightforward syncope attacks, brief seizures or apoplectic phenomena? I shall assume, for the reason that the patient repeatedly fell and injured herself, apparently having at the moment none of the usual protective reflexes against injury, that they were not giddy or vertiginous spells but either epileptiform or apoplectiform attacks. The description is inadequate to make a sharp distinction between these two.

The examination at the first hospital entry disclosed some interesting findings. The patient was picking at the bedclothes, rubbing her hands together, unable to relate the history of her illness, unco-operative and apparently lacking in insight. Further notes point out that she was suspicious and difficult to manage, being emotionally unstable and belligerent. Even though the psychiatric consultant reassures us that the patient was not "demented or psychotic," I do not recognize this as normal. Change in personality, lack of insight, confusion, emotional instability, irritability and suspiciousness are marks of intellectual deterioration due to a disorder of the brain. If acute, it may be on a toxic basis, but if chronic, as it was in this case, it is indicative of structural brain disease often termed an organic reaction type by psychiatrists. These signs, of course, have no specific localizing value but point to a diffuse involvement of the cerebrum.

The symptoms that precipitated the second admission were much more dramatic. Six hours before entry the patient had appeared quite well, and a few hours later she was found in coma. In addition, the extremities were stiff and rigid, the head and eyes deviated to the left, the eyes jerked from side to side, the pupils were unreactive, and the plantar responses were bilaterally extensor. It seems to me that the patient at that time was functioning at

essentially a brain-stem level. The description of the position of the limbs is incomplete, but it is possible that she was assuming postures seen in decerebrate rigidity. The most we can conclude is that there was abrogation of all cerebral function.

There are two possible explanations of the spontaneous nystagmoid movements. There might have been a lesion in the vestibular nuclei or in the connections between these nuclei and the third, fourth and sixth nuclei by way of the medial longitudinal fasciculus. If these nystagmoid movements were always toward one side they might have been caused by a focus of irritation, that is, epilepsy, in the contralateral cerebral hemisphere. I shall assume that the former was the case.

The unreactive pupils are of little localizing value. They could have been Argyll-Robertson pupils or an iridoplegia due to damage of the third-nerve nuclei. Skew deviation was reported. This term applies to a lack of parallelism between the axes of the eyes so that one looks up and outward and the other is deviated down and inward. Skew deviation is usually associated with external ophthalmoplegias but occasionally with lesions of the cerebellum. The best interpretation here is that there was a disorganization of ocular movement at the level of the pons or midbrain.

Slight deviation of the head and eyes to the left requires a word of explanation. Stimulation of the aversive field of Brodmann's† Area 8 of the cerebral cortex causes turning of the head and eyes to the opposite side, and an epileptic focus does the same. Destructive lesions of these areas cause paralysis of contralateral gaze. Also destructive lesions just lateral to sixth nerve nucleus cause paralysis of gaze toward the side of the lesion, and usually a unilateral sixth-nerve palsy as well. I shall assume in this case that the head and eyes were turned to the left because of a disturbance in function at the level of the pons. The nystagmoid movements are an expression of the same disturbance. Here I am treading on dangerous ground, because they might have been due either to a pontine or a midbrain lesion or to a focus of irritation, that is, epilepsy, in the right frontal lobe.

The patient never actually moved her arms and legs except once when they were pricked with a pin. Was there paralysis for voluntary movement? One cannot say because she was comatose. Reflex withdrawal from a painful stimulus may be a spinal-reflex withdrawal and so does not give much assistance. Also, intermittent stiffening of the limbs could have been due to a transient release of postural mechanisms in the lower brain stem. Bilateral Babinski signs in a comatose person may only signify that the motor cortex is disordered as badly as the rest of the brain. I am unable to assume from all this that there was a quadriplegia due to a brain-

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†Brodmann, K. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. 334 pp. Leipzig: J. A. Barth, 1909.

stem lesion, although functionally there undoubtedly was a quadriplegia.

Deep coma lasting four days is always proof of severe brain disease. It can be due to the occlusion of the basilar or one of the other large cerebral arteries, to brain hemorrhage, to any of several metabolic diseases in which insufficient oxygen or glucose is sent to the brain or to repeated convulsions. Again, when interpreted physiologically, it is indicative of either a widespread and severe cerebral disorder or a disease in the vicinity of the thalamus and midbrain.

The temperature of 108°F., the pulse of 160 and the respirations of 50 are of interest. Often in midbrain and pontine lesions the temperature, pulse and respirations rise to great heights, possibly owing to a dysfunction of the heat-dissipating mechanism. Such could be the mechanism here. In comatose patients, however, pulmonary congestion and edema and bronchopneumonia are so frequent that these must always be given first consideration. With a leukocytosis and the x-ray films of the chest showing fine areas of increased density in the left lung field, bronchopneumonia is the likeliest explanation. In comatose patients the ground is always prepared for pulmonary infection, because of the disturbance of pulmonary vasomotor reflexes.

From this part of the discussion I come to the conclusion that we are dealing with a disease that diffusely involved the cerebrum and that the attacks of dizziness were either epileptic convulsions or minor apoplexy. Furthermore, in the last four days of life, there was an almost complete suppression of cerebral function due either to status epilepticus or to a lesion of the midbrain and pons.

Now let us search for the etiologic factor. The blood Hinton and Wassermann and the cerebrospinal-fluid Wassermann tests were positive. The spinal fluid showed increased cells, increased total protein and a first-zone colloidal gold reaction. This is the usual picture of general paresis, but it is not pathognomonic as was once believed. I have seen similar cerebrospinal-fluid findings in asymptomatic and other forms of neurosyphilis. The patient was said to have had congenital syphilis — a statement without proof. I do not believe that a congenital syphilitic patient would live until fifty-five before having symptoms. I know of no older patient than one who developed general paresis at twenty-nine. It is probable that this woman acquired syphilis in adult life, possibly after the birth of her children.

Of course, parietic neurosyphilis could have accounted for the whole picture. It is the obvious explanation of the personality changes, the curious dizzy spells and the nervous prostration. That parietic patients sustain injuries in such spells is well known, and old untreated patients often have subdural hematomas for this reason. These hematomas, now rarely seen, were once thought to be syphilitic.

But what about the final episode? On the basis of neurosyphilis there are two possible explanations: convulsions, since 50 to 60 per cent of paretics have them, and syphilitic basilar arteritis, with thrombosis and infarction. Although tempted at first to conclude that this patient merely went into coma and died of status epilepticus, I am compelled, because of the skew deviation, to assume a vascular lesion of the pons, namely, a thrombosis of the basilar artery with infarction of pons and midbrain. If the eyes were merely roving independently, as they often do in a comatose person, then this diagnosis is probably wrong.

#### CLINICAL DIAGNOSES

Cerebral hemorrhage.  
Central-nervous-system syphilis.

#### DR. ADAMS'S DIAGNOSES

Thrombosis of basilar artery, with infarction of pons.  
General paresis.  
Bronchopneumonia.

#### ANATOMICAL DIAGNOSES

General paresis.  
Bronchopneumonia.

#### PATHOLOGICAL DISCUSSION

DR. CHARLES S. KUBIK: Dr. Adams gave excellent reasons for thinking that this patient had thrombosis of the basilar artery. None was found, however, nor was there occlusion of any of the other main arteries. There was general paresis, with marked involvement of the cerebral cortex. There was also bronchopneumonia.

There was cloudiness of the arachnoid membrane. The convolutions were atrophied only slightly, and there was little enlargement of the lateral ventricles. Microscopically, the subarachnoid space and the perivascular spaces of the small cortical blood vessels were infiltrated with lymphocytes and plasma cells. In the cortex many nerve cells were degenerated; there were numerous rod-shaped microglial cells, and a proliferation of astrocytes. The capillaries and arterioles were prominent and appeared to be increased in number. There was a granular ependymitis of the fourth ventricle.

The findings were characteristic of general paresis. It is interesting that there was little generalized cerebral atrophy.

#### CASE 31012

##### PRESENTATION OF CASE

A forty-five-year-old woman was admitted to the hospital in coma.

Eight days prior to admission the patient complained of a headache, which became so severe the

following morning that she was forced to lie down. Shortly afterward she was found unconscious. The left side was completely paralyzed, there were slight twitchings of the right arm and leg, and the tongue was bleeding from an area where a small piece had been bitten out. The patient remained unresponsive until admission, except for two or three occasions when she said a few words and appeared to understand what was being said to her. The systolic blood pressure when she was found was said to have been 220; it varied between 140 and 180 afterward. The diastolic pressure was unknown, and there was no knowledge of previous hypertension.

The patient had had an "inflamed ovary" removed and an appendectomy nine and three years prior to admission, respectively. She had always bruised easily.

Physical examination revealed an unconscious woman, occasionally moaning and moving the arm and leg on the right but not on the left. There was a "mousey" odor to the breath. The skin and scleras had an icteric tinge. Numerous bruises, petechial hemorrhage and dilated capillaries were present over the extremities and to a lesser extent on the extremities, face, chest and back. The neck was stiff. The heart was slightly enlarged to the left, but there were no murmurs. A mass was palpable in the upper half of the epigastrium, rather more to the left than to the right of the midline. The pupils were of average size and equal and reacted slightly to light. The eyelids were closed, and the eyes were directed straight forward. The fundi were negative except for somewhat tortuous retinal arteries and a certain amount of arteriovenous nicking. The tendon reflexes were active and equal. There were extensor plantar responses bilaterally.

The temperature was 101°F., the pulse 76, and the respirations 16. The blood pressure was 160 systolic, 85 diastolic.

Examination of the blood revealed a red-cell count of 4,090,000, with 12.8 gm. of hemoglobin, and a white-cell count of 9600, with 75 per cent neutrophils, 10 per cent lymphocytes, 14 per cent monocytes and 1 per cent basophils. There was considerable polychromasia, platelets were present in fairly good numbers, and there were no toxic changes in the neutrophils. The clotting time was prolonged. Clot retraction was normal. The urine had a specific gravity of 1.026, with a ++ test for albumin and a sediment containing many red and white cells and occasional clumps of pus. The prothrombin time was 35 seconds (normal, 16 seconds). The blood sugar was 100 mg. per 100 cc., the serum nonprotein nitrogen 37 mg., and the van den Bergh 2.7 mg. direct, and 4.85 mg. indirect.

A roentgenogram of the chest revealed a generalized increase in the vascular markings. Examination of the abdomen showed an area of calcification in the left side of the pelvis that was thought to be a calcified fibroid and a calcified node in the right

lower quadrant. Examination of the skull was unsatisfactory because of the patient's condition.

A lumbar puncture on admission revealed grossly bloody and xanthochromic fluid under an initial pressure equivalent to 300 mm. of water. Its cell count was 10,200 red cells and 598 white cells, of which 513 were neutrophils. The protein was 264 mg. per 100 cc. One week later a second tap revealed clear yellow fluid with a total protein of 153 mg. per 100 cc.; no cell count was done. The spinal-fluid Wassermann test was negative.

The patient became progressively less responsive; the temperature fell to normal, and the pulse rate varied between 70 and 105. She was given 25 per cent, and later 10 per cent, dextrose in water intravenously, together with normal saline solution and vitamins. Four milligrams of Hykinone was administered daily. On the eleventh hospital day the patient began having generalized convulsive seizures, each lasting five to ten minutes. After two or three days, the seizures became milder and the patient began to improve. She became more responsive and began to talk a little. It was thought that a left homonymous hemianopsia could be demonstrated. The mental status continued to improve. On the thirty-fifth hospital day there was some voluntary motion of the left foot and hand. By this time the prothrombin time had gradually fallen to 28 seconds (normal, 20 seconds) and the van den Bergh was 0.6 mg. direct, and 0.9 indirect.

On the thirty-seventh hospital day the patient suddenly had a chill, followed by a rise in temperature to 102.6°F. There was considerable right costovertebral-angle tenderness. The urine sediment contained innumerable red and a few white cells, and a culture was positive for colon bacilli. A blood culture was also positive for colon bacilli. The neck again became stiff, and the patient lost consciousness. The white-cell count rose to 27,700, with 85 per cent neutrophils. Death occurred on the forty-sixth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. JACOB LERMAN: Were the urine examinations done on catheter specimens?

DR. WYMAN RICHARDSON: They included at least one catheter specimen.

DR. LERMAN: I should like to comment on some of the highlights of the clinical findings. Apparently coma occurred a day or so after she became ill and after she developed headache. She had obvious left-sided paralysis, which points to a lesion on the right side of the cerebrum, but she had twitchings on the right, suggesting a more generalized involvement. She had convulsions at home and also while in the hospital. Those in the hospital were general in nature, not limited to one side. Unfortunately, nothing definite can be said about the presence or absence of hypertension. The reading before she came into the hospital suggests hypertension, but



those in the hospital do not. The changes in blood pressure may have been due to changes in spinal-fluid pressure.

There is a note saying that the patient bruised easily, but that really means nothing unless confirmed by physical findings or laboratory data. Many people give such a history, and it is not significant.

On physical examination certain findings, including a "mousey" odor to the breath, suggest liver disease. One can also observe the same odor in patients with severe infection, particularly those with septicemia. She certainly had jaundice and an enlarged organ, which I take to be the liver, primarily because of its location and also because of the presence of jaundice and a moderately elevated van den Bergh reaction. Apparently the left lobe of the liver was enlarged, since the mass was to the left of the midline. Left-lobe enlargement of the liver suggests syphilis. No mention is made of the blood Hinton test, and there is no evidence of syphilis elsewhere, the spinal-fluid Wassermann test being negative. Consequently, syphilis need not be considered.

She had bruises, petechial hemorrhages and dilated capillaries, which may be manifestations of a hemorrhagic disease, such as thrombocytopenic purpura or symptomatic purpura, or of septicemia, such as blood-stream infection with the meningococcus. In the presence of liver disease confirmed by a prolonged prothrombin time, however, one can adequately explain these signs.

The tendon reflexes were active and equal. That is strange because from the description one would expect inequality. The right arm moved; the left arm did not. Bilateral extensor plantar reflexes also indicated generalized injury to the brain rather than localized injury, which we assumed from the description of the patient. Is it possible that she had not yet developed complete evidence of a unilateral cerebral hemorrhage? Seven days had passed, and one would expect complete manifestation of the injury by that time. Since she did have positive Babinski signs, then the evidence of injury was complete. It is hard to reconcile the various reflex changes with a unilateral cerebral lesion. One may assume generalized injury to the brain, such as could be produced by diffuse hemorrhage, or, in addition to a right cerebral lesion, a previous injury to the left cortex, about which we know nothing.

She had slight anemia and polychromasia, the latter indicating excessive stimulation of bone marrow. The number of platelets was normal, which rules out idiopathic thrombocytopenic purpura. The elevated prothrombin time and van den Bergh values fit in with other evidence of liver disease. The urinary findings indicate pyelonephritis or possibly diffuse hemorrhage involving the kidney substance.

DR. RICHARDSON: I ought to give you additional information. The patient had to be on constant drainage.

DR. LERMAN: Then the urinary findings are not of much value, and I shall have to disregard them.

The lumbar puncture yielded a spinal fluid containing a lot of blood, including old blood, as evidenced by the xanthochromic fluid; the white-cell count was high, consistent with irritation produced by the bleeding, and the Wassermann test was negative. There is no mention of organisms; presumably none were found.

The patient lost ground for a while and then improved. The left homonymous hemianopsia points to a lesion posterior to the chiasm on the right side in the optic radiations going to the occipital lobe. This is consistent with the left-sided paralysis that the patient had.

She then had generalized convulsions, some temporary improvement in the prothrombin time and the van den Bergh reaction and, finally, a colon-bacillus septicemia.

It is difficult for me to put all these findings together. Certainly one can rule out thrombocytopenic purpura as the etiologic factor. Could she have had symptomatic purpura as a result of infection? There is not enough evidence in the early part of the history to indicate a general infection. The problem is to explain the development of coma, which was undoubtedly due to extensive cerebral hemorrhage, including subarachnoid hemorrhage, in addition to at least one major lesion on the right side to account for the left-sided paralysis and the left homonymous hemianopsia. One can arrive at this syndrome by various routes.

First, she may have developed jaundice from acute hepatitis, toxic or infectious in nature, which resulted in an elevated prothrombin time and a tendency to diffuse hemorrhage in the skin and brain. Since the process was rather acute and fulminating, the liver damage may have been in the nature of acute or subacute yellow atrophy. The colon-bacillus infection must then be considered as a terminal event, perhaps due to the indwelling catheter, or to a long-standing pyelonephritis that merely spread terminally.

Second, the patient may have had a serious infection with septicemia, type unknown. It might have been a colon-bacillus infection that was not recognized at first. The septicemia produced jaundice and the hemorrhagic tendency. A possible subheading under this mechanism is that the absorption of hemolyzed blood from the sites of hemorrhage caused plugging of bile capillaries sufficient to produce jaundice. In either case, the jaundice did not play any role of importance. Death was due to recrudescence of the original infection.

Third, the patient may have had bacterial endocarditis due not to *Streptococcus viridans* but to the

colon bacillus. Such an infection would explain many of the central-nervous-system findings and even the jaundice. On the other hand, there is no history of pain, which is so frequently associated with the embolic phenomena of bacterial endocarditis, unless, of course, cerebral embolism occurred first and knocked out all conscious sensations. There are no findings in the heart to point to endocarditis. The absence of any information regarding blood cultures until the final culture was obtained steers one away from a diagnosis of endocarditis.

One must also think of such rare conditions as hepatoma, with cerebral manifestations resulting from metastatic involvement of the cerebrum. This would not explain, however, the tendency to skin hemorrhages, unless there was an associated cirrhosis. Rupture of an aneurysm on the right side of the brain could explain all the cerebral findings but not the peripheral findings, such as the tendency to hemorrhage in the skin, and the liver damage.

Thus I am right back to my first thought: namely, this was a patient with jaundice due to acute hepatitis, probably subacute yellow atrophy. The hemorrhagic tendency resulting therefrom then produced cerebral vascular bleeding, diffuse throughout the brain and subarachnoid space, but including one major lesion on the right side. In addition one might suppose that the colon bacilli would localize in the spinal fluid, and also in the areas of cerebral damage.

DR. RICHARDSON: I want to give Dr. Lerman more bits of evidence. In the first place, the capillary dilatation was not diffuse, but true spider-angioma telangiectasis. This was more striking than in any patient I have ever seen — small central red spots with lines radiating in a characteristic spider design, most marked over the chest and abdomen but also present on the arms and elsewhere. I did not tumble to this the first night I saw the patient, but the next morning it seemed important. At that time I also noticed jaundice and the mousey odor to the breath. I thought it was all due to hepatic failure, and in the note I wrote, I said that she had primary liver failure with a bleeding tendency, causing some type of bleeding lesion in the brain. Later I discovered that for many years she had had a high alcoholic intake; in fact, one of the surgeons who had operated on her previously reported that she had had at that time a cirrhosis of the liver. My thought was that she had cirrhosis of the liver with superimposed acute hepatitis and cerebral hemorrhage. I thought the latter was subarachnoid and possibly due to a congenital aneurysm, with more bleeding than normally would have been expected. I did not see the patient at the very end, but I believe that the second episode meant that she had another hemorrhage.

A PHYSICIAN: What about the mass in the epigastrium?

DR. RICHARDSON: I thought that it was the liver, but not entirely the left lobe.

DR. LERMAN: I did not mean to indicate that the mass was entirely due to left-lobe enlargement, but certainly a prominent left lobe points toward syphilis. The additional history indicates extensive chronic liver disease rather than an acute episode of liver disease, and confirms my supposition that the hemorrhagic tendency was due to liver disease. Another possibility, which I think I can dismiss, is the development of a hepatoma in a cirrhotic liver. She could have had a hepatoma with metastases to the brain, and coma could have been produced by hemorrhage into one or more metastases.

DR. JOSEPH C. AUB: Hepatoma rarely metastasizes to the brain. There are a few cases in the literature, but they are unusual.

DR. LERMAN: I thought that a hepatoma metastasized to almost any organ.

DR. AUB: Sometimes to lung, and sometimes brain; but it is rare.

DR. LERMAN: I admit that it is unusual, but I was trying to find one diagnosis to cover all the findings. I shall have to stick to my original diagnosis of hemorrhagic tendency from liver disease.

DR. RICHARDSON: We considered hepatoma in the beginning on the basis of the mass and also because of the polychromasia, but I finally explained the latter in the way Dr. Lerman did, that is, as due to hemorrhage, and discarded the idea of hepatoma.

#### CLINICAL DIAGNOSES

Cerebral hemorrhage.  
Alcoholic cirrhosis of liver.  
Acute hepatitis.  
Septicemia (colon bacillus).

#### DR. LERMAN'S DIAGNOSES

Cerebral hemorrhage, diffuse and right cerebral.  
Subarachnoid hemorrhage.  
Portal cirrhosis.  
Acute hepatitis.  
Septicemia (colon bacillus).  
Pyelonephritis?

#### ANATOMICAL DIAGNOSES

Cerebral hemorrhage, old: right temporal lobe.  
Cerebellar hemorrhage, recent.  
Cerebral infarction, right frontal and parietal, old.  
Toxic cirrhosis of liver.  
Septicemia (colon bacillus).  
Acute pyelonephritis.  
Bronchopneumonia, with abscess formation.  
Petechieae of skin, gastrointestinal tract, pleura, epicardium and endocardium.  
Jaundice.  
Operations: appendectomy and right oöphorectomy, old.

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Before Dr. Kubik tells us what was found in the brain, I shall say

that there was cirrhosis of the liver. It did not look like the ordinary alcoholic type. The nodules varied in size tremendously. The usual case of alcoholic cirrhosis shows uniformly small nodules. These suggested the healed atrophy or toxic type of cirrhosis. We found no evidence of acute hepatitis.

DR. RICHARDSON: She had, however, been in the hospital a long time.

DR. LERMAN: Forty-six days.

DR. CASTLEMAN: She had, as you know, a colon-bacillus septicemia and numerous abscesses to the kidney. I do not know whether the abscesses developed after her admission to the hospital, but she probably had some degree of pyelonephritis before she came in. The lungs were diffusely studded with areas of bronchopneumonia that had broken down and formed abscesses. She had a great deal of infection, which may have accounted in part for the jaundice; that is, the jaundice may have been due to the combination of overwhelming infection and a poorly functioning liver. I do not believe that the liver disease itself was responsible for that amount of jaundice.

DR. RICHARDSON: If you had seen her when she came in, it might have altered your opinion. The liver was acutely involved. She was given tremendous amounts of glucose intravenously.

DR. CASTLEMAN: Did the liver shrink?

DR. RICHARDSON: I cannot remember. I do not see any note to that effect but believe that it did. She began to improve and everyone felt encouraged, and then she had a sudden episode and went down hill.

DR. CHARLES S. KUBIK: Most subarachnoid hemorrhages, as you all know, are due to ruptured aneurysms. We did not find any aneurysm in this case. There was an area of infarction in the right frontal lobe. This probably contributed only slightly to the symptomatology. The main lesion was an old hemorrhage in the right temporal lobe. This hemorrhage, measuring 8 cm. in length, extended practically the whole length of the temporal lobe. It was surrounded by a firm connective-tissue capsule about 0.5 mm. in thickness. There was also a recent hemorrhage in the cerebellum, which unquestionably accounted for the episode that occurred shortly before the patient died and was probably the chief cause of death. It had broken

through into the subarachnoid space. There was but little arteriosclerosis. I am not sure whether the older hemorrhage had leaked into the ventricle or into the subarachnoid space, or into both.

DR. CASTLEMAN: Do you think that this was the usual form of cerebral hemorrhage? May it not have been due to jaundice?

DR. KUBIK: I do not know. I have seen three cases with severe jaundice and cerebral or subarachnoid hemorrhage. The two with cerebral hemorrhages came to autopsy; the one who had a subarachnoid hemorrhage is still living.

DR. CASTLEMAN: This patient's heart weighed about 400 gm., which is not particularly large. Do you think that she had had hypertension in the past?

DR. RICHARDSON: When the story was given to me I was inclined to doubt it.

DR. CASTLEMAN: If we knew that she had not had hypertension, we could blame the hemorrhage on the jaundice.

DR. RICHARDSON: There was just the one reading, taken shortly before she entered the hospital. At the time of one of her previous operations there was no hypertension.

DR. KUBIK: The systolic reading of 220 was obtained after onset of the first hemorrhage, and the elevation might have resulted from increased intracranial pressure.

DR. RICHARDSON: I have had personal experience with three patients with severe liver damage accompanied by severe cerebral bleeding of one sort or another. One had a subdural hematoma that was successfully operated on; the hemorrhage may have been due to trauma, although the amount of bleeding was more than one would expect. At this moment there is a patient in the hospital with severe alcoholic cirrhosis who has probably had some cerebral bleeding. My interpretation is that the bleeding is due to prothrombin lack, although there must be something to precipitate the bleeding.

DR. CASTLEMAN: Is it not also true that a person with as large a cerebral hemorrhage as this would usually have died before there was a chance for a second episode.

DR. KUBIK: Yes; massive cerebral hemorrhages are practically always rapidly fatal, the patient rarely surviving more than a few days.

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## NAVAL MEDICAL OFFICERS

Although the Army of the United States has indicated that its need for medical officers is, for the moment, covered by recent graduates from medical schools who have completed their internships and residencies, an urgent demand for such officers in the United States Navy, whose personnel and activities are constantly increasing, still continues. As noted in a letter published elsewhere in this issue of the *Journal*, the physical requirements for the Navy Medical Corps have been lowered, the age limit has been increased and waivers may be obtained for certain disqualifying physical defects. Undoubtedly the applications of

many physicians were refused because of one of these reasons. Each one of these men, as well as others who believe that their contributions to the war effort would be greater in a service capacity than in civilian practice, should respond to this appeal.

## A SURGEON ON WAR AND PEACE

COLONEL ELLIOTT C. CUTLER, chief consultant in surgery, Army of the United States, European Theater of Operation, and Moseley Professor of Surgery, Harvard Medical School, delivered on May 6, 1944, at St. John's College, Cambridge, England, the Linacre Lecture on the subject "A Surgeon Looks At Two Wars." Colonel Cutler's lecture, in abridged form, has appeared as the leading article in the September 30 issue of the *Lancet*.

The comparison between the types of injuries sustained in this war and their treatment and those of twenty-five years ago is interesting; more important is the apparently considerable increase in psychiatric casualties over those of 1916-1918 despite a more rigid screening at the source, and the theories advanced to explain this experience. Chief among these explanations rank an easier discipline in our army of today, leaving an avenue of escape open for the battle-weary soldier, inferior leadership by subaltern officers, and a loss of self-sufficiency and independence in a country where overpaternalism has softened the population.

In particular, Colonel Cutler emphasizes the military value of hate in carrying a war through to its successful conclusion; he points out that it is a military fault of the English and Americans that they are naturally peace-loving and have as yet found little cause for holding such a personal grudge against the Germans as have the Russians. This hatred we have had cause to develop against the Japanese, and the Japs we are able to hunt down with relentless fury, for their atrocities have been committed against ourselves.

Future opportunities for Germany to fling herself at the throats of civilized mankind must be denied, and Colonel Cutler closes his lecture on the note that those who make the peace must this time be those who have been to war and know what it

means. It is expressly stated that war must be waged in hate, and it is implied that hate must not be forgotten when the peace is made.

In the same issue of the *Lancet* is one of the sanest and most temperate editorials that it has been our fortune to read — an editorial that bespeaks the innate fair-mindedness of the British nation. We are reminded that this war is not between men and a different species, but between men and men, in whom all the human elements are mixed. True, our adversaries have been led into intolerable deeds by their psychologic immaturity, but "five years have not changed our opinion that a peace of understanding has more permanence than a peace of passion."

"The young men who now command our thoughts and bear our hopes," the editorial continues, "are often heroes but seldom fanatics; and for our part we should say that one of their greatest achievements has been to combine military resolution with an objective attitude toward the enemy."

An attempted destruction of Germany will sow the seeds of hate and prepare for a future harvest of calamity. Our only hope is in a modeling of civilization, to help young Germans "feel it an adequate purpose in life to rebuild out of the ruins the Germany of Kant and Goethe and Beethoven — to whom we might add Virchow, Koch and Ehrlich, or others according to taste."

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

ALLEN — Gardner W. Allen, M.D., of Boston, died July 12. He was in his eighty-ninth year.

Dr. Allen received his degree from Harvard Medical School in 1882. He was formerly professor of genitourinary surgery at Tufts College Medical School, and surgeon in the Genitourinary Department of the Boston Dispensary. He was a member of the American Association of Genito-Urinary Surgeons, Massachusetts Historical Society, American Antiquarian Society, Naval Historical Foundation, American Historical Association and the Military Historical Society of Massachusetts.

DAWSON — Raymond J. Dawson, M.D., of Methuen, died November 20. He was in his thirty-ninth year.

Dr. Dawson received his degree from McGill University Faculty of Medicine, Montreal, in 1932. He interned at the Lynn Hospital and Montreal General Hospital, and had practiced in Methuen from 1934 until entering the Army of the United States as a lieutenant in the Medical Corps, from which he was eventually honorably discharged. He was a fellow of the American Medical Association.

His widow, his parents and three brothers survive.

HAWES — Edward E. Hawes, M.D., of Hyannis, died November 30. He was in his eighty-third year.

Dr. Hawes received his degree from the University of Vermont College of Medicine in 1886. He was on the staff of the Cape Cod Hospital.

OSSEN — Emil Z. Ossen, M.D., of Quincy, died December 16. He was in his thirty-ninth year.

Dr. Ossen received his degree from State University of Iowa College of Medicine, Iowa City, in 1931. He was staff physician of the Norfolk County Hospital from 1932 to 1937. He was visiting physician at the Beth Israel Hospital and on the staff of the Quincy City Hospital and the Milton Hospital. He was a fellow of the American Medical Association.

His widow, a son and a daughter survive.

SANBORN — Byron Sanborn, M.D., of Topsfield, died December 20. He was in his seventy-first year.

Dr. Sanborn received his degree from Dartmouth Medical School, Hanover, New Hampshire, in 1900. He served as associate medical examiner for one district of Essex County from 1930 to 1939. He had also served as examining physician for Topsfield public schools and was town medical adviser. He was a fellow of the American Medical Association.

His widow and a son survive.

YOUNG — Evangeline W. Young, M.D., of Framingham, died December 20. She was in her seventy-first year.

Dr. Young received her degree from Tufts College Medical School in 1906. She practiced medicine in Boston until 1934. She was a former member of the Massachusetts Medical Society.

A brother survives.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1944

DISEASES	RÉSUMÉ		
	NOVEMBER 1944	NOVEMBER 1943	SEVEN-YEAR MEDIAN
Anterior poliomyelitis.....	35	24	6
Chancroid .....	2	*	*
Chicken pox .....	1024	1281	973
Diphtheria .....	28	29	14
Dog bite .....	590	592	598
Dysentery, bacillary .....	24	22	30
German measles .....	54	66	39
Gonorrhea .....	445	510	421
Granuloma inguinale .....	1	*	*
Lymphogranuloma venereum .....	2	*	1
Malaria .....	50	25	816
Measles .....	355	816	8
Meningitis, meningococcal .....	31	37	1
Meningitis, Pfeiffer-bacillus .....	3	6	†
Meningitis, pneumococcal .....	3	4	†
Meningitis, staphylococcal .....	0	0	†
Meningitis, streptococcal .....	0	0	†
Meningitis, other forms .....	4	0	†
Meningitis, undetermined .....	2	11	†
Mumps .....	916	399	389
Pneumonia, lobar .....	162	225	234
Salmonella infections .....	4	7	6
Scarlet fever .....	777	704	594
Syphilis .....	420	617	503
Tuberculosis, pulmonary .....	222	215	220
Tuberculosis, other forms .....	11	18	20
Typhoid fever .....	5	6	3
Undulant fever .....	5	6	5
Whooping cough .....	499	405	557

\*Made reportable in December, 1943.

†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

### COMMENT

Poliomyelitis during November showed the expected marked drop in number of cases, there being only a little more than a third of the previous month's cases. Diphtheria, although at a comparatively low point as compared with the levels ten or fifteen years ago, was nonetheless twice the seven-year median for November. There is still plenty of need for stressing immunization.

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Arlington, 2; Ashfield, 1; Boston, 5; Brockton, 1; Colrain, 1; Conway, 1; Dalton, 1; Easton, 2; Fort Devens, 1; Groveland, 2; Haverhill, 1; Holyoke, 1; Lexington, 2; Marlboro, 1; Melrose, 1; Middleboro, 2; New Bedford, 1; Pittsfield, 7; Rockland, 1; Williamstown, 1; total, 55.

Diphtheria was reported from: Ayer, 1; Boston, 2; Danvers, 1; Foxboro, 1; Framingham, 1; New Bedford, 3; Peabody, 2; Somerville, 15; Whitman, 1; Worcester, 3; total, 28.

Dysentery, bacillary, was reported from: Beverly, 2; Boston, 5; Dedham, 1; Everett, 1; Fall River, 4; Lawrence, 1; Lynn, 1; North Andover, 3; Somerville, 1; Stoneham, 1; Winchester, 2; Worcester, 2; total, 24.

Encephalitis, infectious, was reported from: Newton, 2; Quincy, 1; total, 3.

Malaria was reported from: Boston, 2; Camp Edwards, 8; Fort Devens, 16; Cushing General Hospital, 16; Haverhill, 4; Hingham, 1; Woburn, 1; West Bridgewater, 1; Worcester, 1; total, 50.

Meningitis, meningococcal, was reported from: Arlington, 1; Boston, 9; Cambridge, 2; Canton, 1; Chelsea Naval Hospital, 1; Easton, 1; Everett, 1; Falmouth, 1; Framingham, 1; Hardwick, 1; Lowell, 2; Lynn, 1; Medford, 1; Newton, 2; Palmer, 1; Quincy, 2; Watertown, 1; Webster, 1; Weymouth, 1; total, 31.

Meningitis, Pfeiffer-bacillus, was reported from: Lawrence, 1; Springfield, 1; Wellesley, 1; total, 3.

Meningitis, pneumococcal, was reported from: Boston, 1; Cambridge, 1; Springfield, 1; total, 3.

Meningitis, other forms, was reported from: Boston, 2; Milford, 1; Needham, 1; total, 4.

Meningitis, undetermined, was reported from: Auburn, 1; Worcester, 1; total, 2.

Salmonella infections were reported from: Framingham, 1; Medford, 1; Salem, 1; Wellesley, 1; total, 4.

Septic sore throat was reported from: Boston, 10; Holyoke, 2; Marion, 1; Newton, 1; total, 14.

Tetanus was reported from: Beverly, 1; North Attleboro, 1; Quincy, 1; total, 3.

Trichinosis was reported from: Boston, 1; total, 1.

Typhoid fever was reported from: Rehoboth, 1; total, 1.

Undulant fever was reported from: Bridgewater, 1; Lawrence, 1; Mansfield, 1; Somerville, 1; Southbridge, 1; total, 5.

## MISCELLANY

## NOTE

The following physicians were accepted into fellowship in the American College of Surgeons during 1944:

MASSACHUSETTS: Boston — E. L. Carey, P. W. Hugenberger, A. C. Kallan, H. G. Lee, R. E. Mabrey, D. O. McKee, J. J. Michelsen and L. H. Nason; Brookline — J. F. Conway, C. J. Duncan and H. C. Rosen; Brockton — S. F. Peterson; Cambridge — R. W. Smith; Fall River — D. F. Gallery; Norwell — Ralph Heifetz; Norwood — D. J. Collins; Salem — F. P. Morse, Jr.; W' alpole — G. O. Garcelon; Westfield — D. R. Hayes and J. J. Tomasi; Worcester — E. E. Fipphen, E. J. Medden and Adolph Meltzer.

NEW HAMPSHIRE: Epping — W. C. Montgomery; Manchester — D. J. Sullivan and S. W. Yudicky; Nashua — Philip McQuستن.

## CORRESPONDENCE

## NEED FOR NAVAL MEDICAL OFFICERS

To the Editor: The daily casualty reports emphasize the urgent need for medical officers, and the procurement of doctors for the United States Naval Reserve remains a number one priority at this time. A concentrated effort is being made to obtain approximately 3000 physicians in order to increase the efficiency of the present medical forces.

Doctors on the home front are sacrificing many peacetime pursuits in professional and social fields in order to preserve existing medical standards. It is evident, however, that a disproportion of medical personnel exists in many communities throughout the country. In some areas, the number of physicians exceeds the demands, whereas in others there is

a definite shortage. The problem is largely one of redistribution. Each doctor should reach a conscientious decision whether or not he can make a greater contribution in a direct military capacity.

Physical requirements for the Navy Medical Corps have been modified considerably since the beginning of the war. Doctors may now be accepted up to the age of sixty. Those in the older age groups are assigned to naval hospitals, dispensaries, the Veterans' Administration and other naval activities ashore. Organic physical defects continue to be disqualifying, but waivers can be granted for a variety of conditions that were formerly unacceptable.

Without making any definite commitment, applicants may be interviewed at this office without prior appointment on any weekday. Additional pertinent information will be furnished, and individual problems can be discussed.

H. S. GLIDDEN, Commander (NIC), U.S.N.R.  
Senior Medical Officer

Office of Naval Officer Procurement  
150 Causeway Street  
Boston 14

## THE MACHINE AGE

To the Editor: Something grim has happened to society since the opening of the industrial revolution about one hundred and seventy years ago. Much of it should be the concern of the medical sciences.

For several generations there has been abroad in the world the notion that character, culture and contentment can come through the multiplication of machines. This illusion has had a large part in developing the emotions and social unrest which now finds us fighting a second world war.

When the excessive mechanization of society creates such fantastic and swiftly changing environments that distortion and deterioration of standards and values result, man's limited biologic equipment (including his mental, moral and spiritual potentialities) is unequal to the task of making normal peaceful adjustments.

Is this the law of diminishing cultural returns?

What, if anything, can the medical profession do to interpret and correct this pathology?

A. E. P. ROCKWELL, M.D.

241 Grafton Street  
Shrewsbury, Massachusetts

## BOOK REVIEWS

*Tuberculosis of the Ear, Nose and Throat.* By Mervin C. Myerson, M.D. 8°, cloth, 291 pp., with 88 illustrations. Springfield, Illinois: Charles C Thomas, 1944. \$5.50.

Dr. Myerson has had an unusual opportunity to study tuberculosis of the upper respiratory passages at the Sea View and Metropolitan hospitals in New York City. In this book, he draws on his vast experience with more than 10,000 cases for the many salient facts that are presented.

Inasmuch as tuberculosis of the larynx is the lesion most frequently encountered in practice, over half the book is devoted to this disease. Treatment is covered in detail, and the reviewer is in full accord with the methods that are considered beneficial and those that should be discarded. Other chapters briefly consider tuberculosis of the nose, ear, oral cavity, tongue, pharynx and esophagus. Finally, he gives full consideration to tuberculosis of the trachea and bronchi. Recent concepts of tuberculosis of the bronchi, including etiology, diagnosis and pathology, are fully discussed, although its treatment still awaits further study and experience. The illustrations and drawings are excellent and help considerably in visualizing the pathology.

The author is outspoken in his opinions, which, on the whole, are based on sound scientific principles. This book will be invaluable to otolaryngologists, as well as to all men interested in the problem of tuberculosis.

*Intravenous Anesthesia.* By R. Charles Adams, M.D., C.M., M.S. (Anes.). 8°, cloth, 663 pp., with 75 illustrations. New York City: Paul B. Hoeber, Incorporated, 1944. \$12.00.

With the ever-widening fields of usefulness of intravenous anesthetics, this book is most timely. Dr. Adams is to be congratulated on the comprehensive manner with which he

has treated this subject. The book should be read by every anesthesiologist, and it will make a useful addition to any surgical library.

The chapters dealing with the history of intravenous apparatus, methods and agents are excellent, being particularly valuable to those interested in the history of medicine. The fact that the historical aspects of intravenous methods are so well covered does not mean that the practical side of the subject has been neglected. About two thirds of the book are devoted to the barbituric acid derivatives, this being the group of drugs that has proved the most practical for intravenous anesthesia.

The chapter on the technic of intravenous injection is especially to be recommended. It contains many suggestions that will prove helpful to anyone who is called on to do venipuncture, whether or not for the administration of an anesthetic agent.

The appropriateness of the chapter on analeptics is well stated in its opening sentence, "It seems appropriate after detailed discussion of the depressant drugs such as the derivatives of barbituric acid, particularly their effect on respiratory function, to consider, at least briefly, the value of respiratory stimulants and analeptics in combating the depressing effects of these drugs."

The final chapter, which discusses intravenous anesthesia for military surgery, is timely, and Dr. Adams was wise in covering this aspect of the subject in a separate and final chapter, thus making for a more general and prolonged usefulness of the book.

The bibliographies after each chapter are extensive.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Allergy in Practice.* By Samuel M. Feinberg, M.D., associate professor of medicine and chief of the Division of Allergy, Northwestern University Medical School. With the collaboration of Oren C. Durham, chief botanist, Abbott Laboratories. Chicago: The Year Book Publishers, Incorporated, 1944. \$8.00.

This new work on allergy has been written for the benefit of not only allergists but also of practicing physicians. The arrangement of the book is practical, since the clinical parts of the text are set in type of normal size, and controversial and other material are in smaller type. In the work are embodied Dr. Feinberg's investigations on fungi allergy, as well as the thirty years' experience of Dr. Durham on pollens and pollen allergy. In addition to asthma and hay fever, many other allergies, including sensitivity, are adequately discussed. Diagnosis and treatment are especially emphasized.

*The Dental Treatment of Maxillo-Facial Injuries: With supplementary material on cases and techniques.* By W. Kelsey Fry, M.C., M.R.C.S., L.R.C.P., L.D.S., R.C.S. (Eng.), consulting dental surgeon to the Royal Air Force, consulting dental surgeon to the Ministry of Health, and dental surgeon to Guy's Hospital; P. Rae Shepherd, L.D.S., R.C.S. (Eng.), dental surgeon, East Grinstead Maxillo-facial Unit; Alan C. McLeod, D.D.S. (Penn.), B.Sc. (dent.) (Toronto), L.D.S., R.C.S. (Eng.), dental surgeon, East Grinstead Maxillo-facial Unit; and Gilbert J. Parfitt, M.R.C.S., L.R.C.P., L.D.S., R.C.S. (Eng.), dental surgeon, East Grinstead Maxillo-facial Unit. With a foreword by Professor F. R. Fraser, M.D., F.R.C.P., director general, Emergency Medical Service, and a section on fractures of the middle third of the face by A. H. McIndoe, M.S., F.R.C.S., F.A.C.S., consulting plastic surgeon to the Royal Air Force, and surgeon-in-charge, East Grinstead Maxillo-facial Unit. 8°, cloth, 434 pp., illustrated. Philadelphia: J. B. Lippincott Company, 1944. \$6.50.

This is an American edition of an English work published in two parts and comprising lectures and demonstrations given to members of the English armed forces at East Grinstead Maxillo-facial Centre. The purpose of this work

is to provide simple instruction in the treatment of injuries of the face as it concerns the dental surgeon.

*The Romance of Medicine: The story of the evolution of medicine from occult practices and primitive times.* By Benjamin L. Gordon, M.D., attending ophthalmologist, Shore Memorial Hospital, Somers Point, New Jersey, and Atlantic County Hospital for Tuberculosis, Northfield, New Jersey. 8°, cloth, 624 pp., with 145 illustrations. Philadelphia: F. A. Davis Company, 1944. \$5.00.

This new work on the history of medicine emphasizes primitive medicine and its relation to the development of modern medicine. The author believes that modern medicine and modern customs are truly an evolutionary development of ancient animistic beliefs, and he has attempted to present a readable but comprehensive account of the ideas alike in the state of health and disease of our savage, semicivilized and civilized ancestors: what their thought was concerning embryology and anatomy, their ideas of the controlling forces governing the human mechanism, their concepts of the mind and soul, and the role it was assumed to play in the human economy.

## NOTICES

### HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held at the Peter Bent Brigham Hospital on Tuesday, January 9, at 8:15 p.m.

### LAWRENCE CLINIC

The Lawrence Clinic has recently been reorganized. Captain G. F. Clark, U.S.N. (retired) will direct the Clinic, and arrangements have been made with the Executive Committee of the Lawrence General Hospital, composed of Drs. Harold R. Kurth, Rolf C. Norris, John J. Hartigan, Z. William Colson, Richard J. Neil and Percy J. Look, whereby the staff of the Lawrence General Hospital will act as the staff of the Lawrence Clinic. When the work of the Clinic increases and more physicians and dentists become available, the program of services will be modified accordingly.

### NATIONAL CONFERENCE ON MEDICAL SERVICE

Postwar distribution of medical care will be the theme for the nineteenth annual session of the National Conference on Medical Service to be held in the Red Lacquer Room of the Palmer House, Chicago, on Sunday, February 11, 1945. Medical legislation, physical-fitness programs, the rehabilitation of veterans, the latest word from the Washington front and the relation between labor and farm groups and medicine are among the topics to be discussed by nationally known speakers. Also listed on the program will be an open discussion on prepayment medical plans, the principal advantages and defects of both service and indemnity types of insurance being presented. Congressman Arthur L. Miller, of Nebraska, author of the Miller Bill to unify certain health services, is to be among the speakers. All members of the American Medical Association are invited to attend. Detailed programs of the conference are now ready and may be obtained by writing to Cleon A. Nafe, M.D., secretary, National Conference on Medical Service, 822 Hume Mansur Building, Indianapolis 4, Indiana.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 11

##### FRIDAY, JANUARY 12

\*9:00-10:00 a.m. Cancer of the Pancreas and Ampulla Relative to Diagnosis and Resection. Dr. Richard B. Cattell. Joseph H. Pratt Diagnostic Hospital.

10:50 a.m. Malignant Tumors. Dr. George E. Morris. (Postgraduate clinics in dermatology and syphilis.) Dowling Amphitheater, Boston City Hospital.

##### SATURDAY, JANUARY 13

\*10:00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

##### MONDAY, JANUARY 15

\*12:00 m.-1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

(Notices continued on page xxii)

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## BACTEROIDES INFECTIONS\*

### An Analysis Based on a Review of the Literature and a Study of Twenty Cases

WILLIAM E. SMITH, M.D.,† AND MARIAN W. ROPES, M.D.‡

BOSTON

THE gram-negative anaerobic bacilli that do not bear spores have been grouped together in a genus to which the name "Bacteroides" has been assigned.<sup>1</sup> There are many reports of human infections caused by Bacteroides, but the occurrence of such cases is not widely appreciated. During the last four years, 20 cases have been seen at this hospital (Table 1). On the basis of cases reported in the literature and those seen here, an attempt will be made to describe the clinical aspects of these in-

fections, with the purpose of calling attention to the various conditions in which Bacteroides infection should be suspected.

and joints. The occurrence of metastatic abscesses makes the prognosis extremely grave. The classification of species within the genus Bacteroides is discussed at the end of this paper. It should be noted that the Bacteroides do not include the anaerobic bacilli of the Dialister and Fusiformis groups, which are at present preserved as separate genera,<sup>1</sup> the one because of the small size of the organisms composing it, the other because of the characteristic pointed shape of its members. Detailed data concerning the many known strains of Bacteroides have been compiled by Weinberg, Nativelle and Prévot.<sup>5</sup> Recently, Dack<sup>6</sup> has published a review of the Bacteroides of medical importance. In studies of strains recovered in this laboratory, a form of bacterial reproduction different from simple fission and associated with the production of anaerobic pleuropneumonia-like colonies as variant growth forms (L-type variation) has been encountered in certain instances. These studies have been presented elsewhere.<sup>7-11</sup>

TABLE 1. *Bacteroides* Infections Seen at the Massachusetts General Hospital, 1939-1943.

TYPE OF INFECTION	NO. OF CASES	RESULT	
		DIED	SURVIVED
Septicemia arising from tonsillar abscess ..	1	1	
Septicemia arising from abdominal abscess ..	1		1
Meningitis arising from chronic otitis media ..	5	1	4
Peritonitis arising from ruptured appendix ..	3		3
Peritonitis arising from salpingitis .....	1		1
Liver abscess after colectomy .....	1	1	
Kidney abscess .....	1		1
Chronic otitis media .....	2		2
Chronic cervicitis .....	2		2
Chronic prostatitis .....	2		2
Skin infection .....	1		1
Totals .....	20	3	17

## BACTEROIDES SEPTICEMIAS

Bacteroides septicemias usually arise following throat infections, otitis media and mastoiditis, surgery or infections of the large bowel or genitourinary tract and war wounds. Etiologically, these septicemias may be divided into two groups. The first and more frequent are the cases caused by the *Bacteroides funduliformis* group of organisms, markedly pleomorphic bacilli characterized by the formation of large bodies (spheres) and filaments on cultivation in artificial mediums. These cases frequently develop metastatic abscesses and carry a high mortality. Pus from the abscesses is usually thick, greenish yellow and somewhat foul but not putrid. The organisms are present in large numbers and may readily be detected in smears as small gram-negative bacilli. The second, and less frequent, group of cases are caused by *Bact. fragilis* or other nonpleomorphic Bacteroides. These cases usually run a less fulminating course, with less tendency to

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the formation of metastatic abscesses. Their prognosis is less grave, only 3 of 8 reported cases having had a fatal termination.<sup>12</sup>

#### *Following Throat Infections*

Excellent clinical and pathologic studies of *Bact. funduliformis* septicemias following throat infections have been presented by Lemierre<sup>13</sup> and by Pham Huu Chi.<sup>14</sup> Among 16 cases, 13 were fatal. The close similarity of Case 1 of the present report and that recently described by Brown, Williams and Herrell<sup>15</sup> to the cases reported by these authors is striking. The cases usually occur in previously healthy persons between twenty and thirty years of age. The onset is sudden, with a chill and high fever, usually on the fourth or fifth day of a pharyngitis, tonsillitis or peritonsillar abscess. The local infection in the throat may appear mild or severe. Chills may recur frequently. Multiple abscesses in the lungs, liver and joints and a serous or purulent pleurisy may develop. Jaundice is frequently observed. A moderate anemia, with a red-cell count of 3,800,000 to 2,800,000, and a polymorphonuclear leukocytosis, with a white-cell count of 14,000 to 22,000, are encountered. In acute cases death may follow within a week.

Joint metastases occurred in 8 of 12 cases, chiefly involving large joints, such as the elbow (4 cases) scapulohumeral (4 cases), knee (3 cases) and hip (1 case).<sup>14</sup> Except for the sternoclavicular joint, which was involved in 2 cases, the smaller articulations were spared. Recovery without ankylosis occurred in 1 case following incision and drainage of two joints and a spontaneous resorption of the effusion in a third. *Bact. funduliformis* was seen in smears of the pus obtained from these joints and was recovered in cultures. Joint involvement — of the hip — was also seen in 1 of the 2 fatal cases of septicemia with *Actinomyces necrophorus* reported by Cunningham.<sup>16</sup> According to Dack,<sup>6</sup> this organism may be identical with *Bact. funduliformis*.

#### *Following Chronic Otitis Media and Mastoiditis*

*Bacteroides* septicemias arising from chronic otitis media and mastoiditis have been reported. Of 2 cases due to *Bact. fragilis*, 1 resulted in recovery.<sup>17</sup> In 1 case due to *Bact. funduliformis* there developed osteomyelitis of the femoral head with abscess in the hip joint.<sup>18</sup> This patient recovered after drainage of the joint and sequestrectomy of the femoral head. It could not be determined whether the infection had arisen in the bone and extended into the joint or vice versa. From a case reported by Rist,<sup>19</sup> it appears that *Bacteroides* infection of a joint may destroy the cartilage and invade the bone or spread through the synovial tissues to present itself as a subcutaneous abscess.

#### *Following Surgery of Large Bowel*

A series of *Bact. funduliformis* septicemias following surgery of the large bowel has been reported from the Mayo Clinic. In 1934, Beaver, Henthorne and Macy<sup>20</sup> described a fatal case following colostomy for carcinoma of the rectum. In the same paper they described another case, which, in the light of Lemierre's cases,<sup>13</sup> appears to have originated from an upper respiratory infection. In 1937, Dixon and Deuterman<sup>21</sup> reported 5 proved cases and 1 presumptive case, all of which followed operations for carcinoma of the large bowel. A fatal termination ensued in the 5 cases in which *Bact. funduliformis* was cultivated from the blood. Multiple abscesses in the liver and lungs were observed at autopsy. Pyelophlebitis was found in 3 cases. The authors concluded that *Bact. funduliformis* septicemia should be suspected when postoperative convalescence is interrupted by a chill, fever, profuse sweating and jaundice. In Case 4 of the present series, *Bacteroides* were recovered in mixed culture from a liver abscess in a man dying of sepsis after colectomy. In Case 2, a *Bacteroides* septicemia arose from an abdominal abscess.

#### *Following Infections of Genitourinary Tract*

*Bacteroides* septicemias arising from the genitourinary tract have been observed in cases of septic abortion and of puerperal sepsis and in postoperative infections. *Bact. fragilis* was cultivated from the blood of 2 women with chills and fever following abortion.<sup>17, 22</sup> Metastatic abscesses did not develop, and both women recovered within a week. *Bact. fragilis*, however, has been cultivated from the blood in a fatal case of post-partum septicemia with liver abscess.<sup>23</sup> Two fatal cases of *Bacteroides* septicemia following operations have been reported by Thompson and Beaver,<sup>24</sup> who<sup>25</sup> have since identified the strains from both cases as *Bact. funduliformis*. Both cases occurred in elderly men, one of whom had suprapubic drainage for carcinoma of the bladder, and the other of whom underwent prostatectomy and removal of stones from the bladder. Chills, fever and leukocytosis appeared ten to eighteen days postoperatively, and death occurred after five to six days of fever. Multiple abscesses were found in the lungs.

#### *Following Infected Wounds*

*Bacteroides* septicemias arising from wounds were observed by Bogdán<sup>26</sup> in Hungary during World War I in soldiers with gunshot wounds involving bones, that is, deep wounds in which conditions were favorable for the development of anaerobic infections. In some cases infection around the wound seemed slight, whereas in others it progressed to gangrene or thrombophlebitis. The onset of septicemia was marked by the appearance of chills and

fever in soldiers who had appeared to be making a satisfactory convalescence. There was severe pain over the region of the liver, with radiation to the right shoulder. Jaundice was frequently noted. The course of the disease was punctuated by the development of metastatic abscesses in the liver, lungs, spleen and joints. Of 24 patients, 16 died after illnesses of about two weeks. These *Bacteroides* wound infections appeared to spread from one patient to another, since all occurred in two nearby hospitals and appeared in rapid succession until the transmissibility of the disease was recognized and greater precautions were taken in treatment of the wounds.

Buday<sup>27</sup> demonstrated that the etiologic agent in a similar series of wounded soldiers with septicemias was a *Bacteroides*, which has since been known as *Bact. pyogenes anaerobius*. The presence of serum in the medium was necessary for growth. Buday's bacillus was closely similar to *Bact. funduliformis* and was placed by Weinberg et al.<sup>5</sup> in that group.

CASE 1.\* A 22-year-old man was admitted on June 6, 1939, with a complaint of chills, fever, headache and sore throat of 14 days' duration. He had previously been in good health. Several days after the onset of the illness, a tonsillar abscess had broken down spontaneously. On admission, the temperature was 105.6°F., the pulse 125, and the respirations 28. The patient appeared to be very ill. Both tonsils were hypertrophied and covered with a profuse, thick, white exudate. There were enlarged lymph nodes at the angles of the jaw. The remainder of the physical examination was not remarkable.

The patient was desperately ill throughout the hospital course and exhibited a septic temperature, with daily excursions between 101 and 106°F. The pulse ranged between 110 and 150. He was given sulfanilamide for 4 days, with a resulting blood level of 13.3 mg. per 100 cc., but the drug was discontinued because of the appearance of jaundice, which became steadily deeper. On the 5th day, fluctuation was observed over the right acromioclavicular joint. Incision and drainage of this joint yielded 60 cc. of thick, creamy-yellow pus containing innumerable gram-negative bacilli and 530,000 white cells per cubic millimeter, 95 per cent of which were polymorphonuclear leukocytes. The left arm became swollen and painful, and crepitus due to gas in the tissues was noted. An extensive abscess developed involving the entire left elbow and upper arm. This was incised and drained on June 19. The patient died on June 22, a month after the onset of his illness.

On admission, the white-cell count was 15,500, with 82 per cent neutrophils. The red-cell count was 4,600,000, and the hemoglobin 90 per cent. The urine gave a ++ test for albumin. Despite repeated transfusions, the red-cell count fell to 1,940,000. The serum bilirubin level (van den Bergh reaction) rose from 10.1 mg. per 100 cc. (biphasic) on June 9 to 51.8 mg. (direct) on June 20.

**Bacteriology.** Blood cultures and cultures of pus from the right acromioclavicular joint were made in meat tubes during life. Gram-negative bacilli were cultivated from both sources. Broth cultures exhibited diffuse turbidity, with production of gas and a foul odor. Colonies on ascitic agar plates were smooth, yellowish white and convex with an entire edge and attained a diameter of 1.0 to 1.5 mm. after 48 hours' incubation. Colonies on blood agar plates were nonhemolytic. The organisms were markedly pleomorphic in size and shape, producing long filaments and large, round bodies. They were strictly anaerobic. Neither spores, capsules nor motility was seen. A young pleuropneumonia-like growth (L-type variation) was observed beneath and near some of the bacterial colonies.<sup>11</sup> Owing to its marked pleomorphism, this strain has been placed in the *Bact. funduliformis* group.

\*We are indebted to Dr. L. Dienes and Dr. E. R. Sullivan for permission to report this case.

CASE 2. A 26-year-old nurse delivered a normal baby (her first child) on September 30, 1941. The day after delivery she had a chill with a temperature of 105°F. There was spasm and tenderness in the left lower quadrant. On the following day, 250 cc. of foul, thin pus gushed from the rectum. Sulfadiazine was given for 4 weeks, with a dosage of 6 to 3 gm. a day. The temperature ranged between 101 and 103°F. for 1 week, after which it remained normal for 4 days. Following this, there was another chill and 4 more days of fever. The patient completely recovered and was discharged on November 1, 1941. The infection was believed to have originated from an abscess that ruptured into the bowel.

The white-cell count ranged between 13,250 and 11,800, with 88 per cent neutrophils. The red-cell count remained about 3,500,000, and the hemoglobin about 65 per cent. The urine was not remarkable. The blood level of sulfadiazine ranged from 4.6 to 10 mg. per 100 cc.

**Bacteriology.** One half to 1 cubic centimeter of blood taken on two occasions while the patient was having a chill was inoculated into four meat tubes. Growth was obtained on both occasions. Diffuse turbidity occurred, with the production of a small amount of gas, which did not have a particularly foul odor. Colonies on ascitic agar plates were smooth, grayish white and convex with an entire edge and attained a diameter of 1 mm. after 48 hours' incubation. Colonies on blood agar plates were nonhemolytic. The organisms were small gram-negative bacilli 1.5 to 2 microns in length and quite regular in size and shape. They did not produce large bodies, and L-type variation was not observed. They were strictly anaerobic. Neither spores, capsules nor motility was seen. Owing to its nonpleomorphic character, this strain was placed in the *Bact. fragilis* group.

Cases 1 and 2 bear out the impression gained from the literature of the greater severity of septicemias due to the pleomorphic *Bacteroides* (*Bact. funduliformis* group) than of those due to *Bacteroides* of uniform morphology (*Bact. fragilis* group). Sulfanilamide did not appear of value in Case 1 during the four days it was given. The prompt recovery in Case 2 was probably due to spontaneous perforation and drainage of the abdominal abscess. It is impossible to determine whether sulfadiazine was of value, since comparable recoveries in previously cited cases of septicemia due to nonpleomorphic *Bacteroides* occurred without drug treatment.

The jaundice that led to the discontinuance of the drug in Case 1 may well have been a result of the infection. In fact, jaundice is so frequently seen in *Bact. funduliformis* septicemias that its occurrence should be regarded as evidence in favor of liver abscess rather than drug intoxication, especially when other signs of drug intoxication are lacking.

Gas in the tissues, as noted in Case 1 and in a previously cited case<sup>16</sup> is occasionally a point of value in differential diagnosis. All the strains encountered in this study produce gas in cultures.

The treatment of *Bacteroides* septicemias corresponds to that of other septicemias arising from focal infections and producing metastases. Appropriate surgical procedures, such as drainage of pus and ligation and excision of affected veins, are the important factors. A case has already been cited of recovery following drainage of metastatic joint abscesses and another following sequestrectomy of an infected bone. Rib resection and drainage was followed by recovery of 2 out of 3 patients with *Bact. funduliformis* empyema occurring after upper

respiratory infection.<sup>26</sup> Buday<sup>27</sup> noted that the only recoveries in his group of soldiers occurred when liver abscesses perforated the lung and drained through the bronchi. There is a recent report of recovery from postanginal *Bact. funduliformis* septiemia following excision of the internal jugular vein on the side of the affected tonsil.<sup>29</sup> None of these patients received sulfonamides.

Sulfonamides have been used in 2 reported cases. A patient with *Bact. funduliformis* liver abscess recovered following sulfathiazole therapy and surgical drainage.<sup>30</sup> Another with postanginal *Bact. funduliformis* septiemia was treated with sulfapyridine and recovered.<sup>15</sup> This drug was said to have affected the course favorably, but the major factor was apparently rib resection with drainage of an empyema. There is therefore no adequate clinical evidence that sulfonamides are of value. Animal experiments, however, indicate that sulfanilamide inhibits the spread of abscesses produced by subcutaneous injections of *Bacteroides* cultures<sup>31</sup> and effectively controls septicemias produced by intravenous injections.<sup>32</sup>

#### BACTEROIDES MENINGITIS

Between 1898 and 1939, at least 11 cases of *Bacteroides* meningitis were reported. Brain abscesses were present in 4 of these. All the cases were fatal, and all arose from chronic otitis media except one of brain abscess that occurred in a patient with bronchiectasis. Between 1940 and 1943, 5 cases of *Bacteroides* meningitis have been seen at the Massachusetts Eye and Ear Infirmary. All arose from chronic otitis media that had extended into the mastoid or labyrinth. Brain abscess occurred in 2 cases.

The onset of *Bacteroides* meningitis is acute, and the symptoms and course are similar to those of meningitides caused by other pyogenic organisms. In smears of spinal fluid, the organisms may be seen as small gram-negative bacilli lying within the cells or extracellularly. They may be mistaken for influenza bacilli. Diagnosis depends on cultivation of the organisms, and meat tubes enriched with ascitic fluid have proved highly satisfactory for this purpose. In one patient, organisms could not be found in direct smears of the spinal fluid but were recovered in cultures. Such a case might have been regarded as so-called "sterile meningitis" if anaerobic cultures had not been repeatedly made. Cultures should be held at least two weeks before being discarded as sterile.

In view of the uniformly fatal outcome of all previously known cases, it was of considerable interest that 4 of the 5 patients in this series recovered. Early and adequate surgical drainage, repeated lumbar punctures and the use of intravenous fluids and transfusions appeared to be the major factors in aiding recovery, but there was evidence that sulfadiazine was a useful adjunct in a patient who had

three separate episodes of meningitis, each of which subsided promptly on administration of the drug. Detailed reports of these cases have already been published.<sup>33, 34</sup>

#### BACTEROIDES PERITONITIS

*Bacteroides* are among the most frequent organisms in human feces, being present in 90 per cent of stools,<sup>3</sup> often in greater numbers than the colon bacillus.<sup>35</sup> It is therefore to be expected that *Bacteroides* will be present in the peritoneum when leakage from the bowel has occurred. In the classic studies of Veillon and Zuber,<sup>36</sup> various species of *Bacteroides* were recovered from the peritoneum in a score of cases of gangrenous appendicitis, and these authors concluded that *Bacteroides* were the most frequent organisms in this condition.

There are many subsequent accounts of strains isolated from the peritoneum.<sup>5</sup> Most strains were recovered at autopsy, but it should not be inferred that the cultivation of *Bacteroides* from the peritoneum necessarily confers an unfavorable prognosis. We have cultivated them during life from 5 patients, only 1 of whom died. Among 3 patients with gangrenous appendicitis yielding *Bacteroides*, 2 recovered uneventfully. Case 5 is cited as an example. The third (Case 3) developed a subdiaphragmatic abscess that yielded a pure culture of *Bacteroides*. As described in the section on septiemia, thrombophlebitis and invasion of the blood stream by *Bacteroides* with formation of liver and lung abscesses may arise from abdominal infections. In Case 4, the patient died, having developed an abdominal abscess and a liver abscess following colectomy.

Peritonitis resulting from leakage from the bowel is of course a mixed infection. It was therefore of interest to encounter a case of peritonitis from which *Bacteroides* were isolated in pure culture. In this patient (Case 6), the peritonitis arose from a salpingitis and, although extensive, subsided within a few days. Clinically, it simulated gonococcal peritonitis.

**CASE 3.** A 53-year-old laborer was admitted on June 27, 1941, with a ruptured appendix and peritonitis. Following operation, he remained in the hospital for 8 months with a pelvic abscess that continued to drain pus through a fecal fistula. Jaundice appeared in November but gradually cleared. In December, a subdiaphragmatic abscess developed on the left and was drained surgically. Treatment included sulfadiazine and sulfathiazole, as well as transfusions. The patient improved slowly and was discharged to a nursing home in March, 1942.

The white-cell count ranged from 5400 to 13,400, and the red-cell count from 2,900,000 to 4,700,000. The serum bilirubin level (van den Bergh reaction) in November was 14.6 mg. per 100 cc. (biphasic).

**Bacteriology.** Pus from the ruptured appendix and fecal fistula yielded *Bacteroides*, *Escherichia coli*, alpha-hemolytic and nonhemolytic streptococci, *Staphylococcus aureus* and several species of Clostridia—the flora of the colon. Abdominal fluid withdrawn in November because of ascites yielded many colonies of *Bacteroides* and anaerobic diphtheroids and a few colonies of alpha-hemolytic streptococci. This fluid was not purulent. Pus from the subdiaphragmatic abscess yielded a pure culture of *Bacteroides*. The Bac-

teroides from this case possessed morphologic and cultural characteristics similar to those of the strain from Case 2 and were regarded as *Bact. fragilis*.

**CASE 4.** A 63-year-old factory worker had an ileotransverse colostomy on April 27, 1941. A right colectomy for removal of carcinoma of the ascending colon was done 11 days later. A right-gutter abscess and fecal fistula developed. The temperature, which had ranged between 100 and 102°F., suddenly began to spike to 103 and 105°, and tenderness was noted over the anterior right costal margin. Sulfapyridine therapy (6 gm. a day) was instituted, but the patient died 1 week after the onset of the spiking fever — 23 days after the colectomy.

**Autopsy.** In the right flank there was a large abscess cavity into which fecal material was leaking from the blind end of the transverse colon. The right lobe of the liver contained a multiloculated, necrotic abscess filled with greenish-yellow pus of foul odor. No evidence of thrombosis was found in the portal circulation. There was an area of bronchopneumonia in the right lower lobe.

**Bacteriology.** A blood culture taken during life grew alpha-hemolytic streptococci. Pus from the abscess yielded *Esch. coli*, *Staph. aureus* and nonhemolytic streptococci. Anaerobic cultures were not made. Culture of the heart's blood at autopsy yielded diphtheroids that were regarded as contaminants. Pus from the liver abscess yielded an abundant growth of *Bact. fragilis* in mixed culture with *Proteus vulgaris* and nonhemolytic streptococci.

**CASE 5.** A 37-year-old chauffeur was admitted on May 31, 1941, with abdominal pain of 4 days' duration. At operation a necrotic appendix was found in the center of a large abscess cavity. Sulfanilamide was placed in this cavity, and cigarette drains were inserted. Sulfapyridine (6 gm. a day) was given for 5 days. The patient improved steadily and was discharged well after a stay of 1 month in the hospital. A fecal fistula healed solidly 1 month after discharge.

**Bacteriology.** Pus taken at operation from the appendiceal abscess yielded an abundant growth of *Bact. fragilis*, *Esch. coli* and a few colonies of alpha-hemolytic streptococci.

**CASE 6.\*** A 50-year-old, unmarried woman was admitted on December 21, 1940, because of lower abdominal pain of 18 hours' duration. There was boardlike rigidity in both lower quadrants of the abdomen. The temperature was 100.5°F., and the pulse 90. Sulfathiazole (1 gm. every 4 hours) was given for 6 days. The temperature fell to normal within 3 days, the pulse remaining around 90. X-ray examination showed many dilated loops of small bowel, suggesting obstruction, and exploratory laparotomy was performed 3 days after admission. The bowel was diffusely coated with creamy-yellow pus, and a large amount of pus was found in the pelvis. There was no perforation or obstruction of the bowel. The right tube appeared normal. There was hydrosalpinx on the left. The abdomen was closed without drainage. The patient appeared quite well after 1 week.

Total hysterectomy, bilateral salpingectomy and right oophorectomy were done 2 weeks later. The right tube was filled with milky fluid and purulent exudate. The right ovary contained many cysts filled with milky fluid. The patient made an uneventful recovery and was discharged well on February 9.

The gonococcus complement-fixation test was negative. The white-cell count fell from 28,700 on admission to 9300 several days later, with a corresponding fall in neutrophils from 92 to 61 per cent. The red-cell count rose from 3,860,000 to 4,870,000. The urine gave a + test for albumin but was otherwise negative.

**Bacteriology.** Cervical cultures were negative for gonococci but yielded an abundant growth of aerobic pleuropneumonia-like organisms. Aerobic cultures of pus obtained from the peritoneum at the first operation remained sterile, but on anaerobic horse-serum-agar plates and semisolid rabbit-serum agar *Bact. funduliformis* was isolated. On anaerobic plates a few pleuropneumonia-like colonies also developed. Subcultures of this strain of *Bacteroides* showed that it produced anaerobic pleuropneumonia-like (L) colonies as variant growth forms. The organisms may have been present in the tissues in the L form, since direct smears of the pus revealed no ordinary bacilli, but the polymorphonuclear

leukocytes were distended by masses of small granules. Photographs and studies of this bacillus and its relation to the L forms have been published elsewhere.<sup>11</sup>

As stated above, the cultivation of *Bacteroides* from the peritoneum may be expected in cases in which there has been leakage from the bowel and should not necessarily confer an unfavorable prognosis. The participation of these organisms in intra-abdominal infections should be borne in mind, however, and anaerobic blood cultures should be made in cases of peritonitis exhibiting septic fever or jaundice.

### LOCALIZED BACTEROIDES INFECTIONS

Like other natural inhabitants of mucous membranes, the *Bacteroides* may give rise to or participate in localized infections in or near these sites, being found either in pure culture or together with other organisms. As described in preceding sections, generalized *Bacteroides* infections may arise from such localized processes.

An extensive but neglected study on the bacteriology of otitis media was made in 1900 by Rist,<sup>37</sup> who concluded that the *Bacteroides* played an important role in chronic suppurative otitis media, particularly in cases with foul-smelling discharge, whereas ordinary pyogenic cocci were the most important agents in acute otitis. We have cultivated *Bacteroides* from 2 patients with chronic suppurative otitis media.

*Bacteroides* have been recovered from various urinary infections in males and females, from cervicitis and Bartholin abscesses<sup>4, 38</sup> and from the lochia of women with post-partum fever.<sup>39</sup> We found them in mixed culture in 3 women with chronic endocervicitis and in 2 men with chronic prostatitis. *Bact. funduliformis* was recovered in pure culture from the pus of a kidney abscess (Case 7). A discussion of the distribution of these organisms in the healthy female genital tract and in genitourinary infections is given at the end of Rist's paper.

*Bacteroides* have been cultivated from lung abscesses.<sup>40</sup> Dack<sup>6</sup> believes that they may be of importance in chronic ulcerative colitis, either as primary agents or as secondary invaders. They have been found in abscesses on the hands of persons who had scratched the skin while working with material from animals infected with *Actinomyces necrophorus* (presumably *Bact. funduliformis*).<sup>5, 6</sup> Such abscesses are usually small and self-limited. We repeatedly recovered *Bact. funduliformis* in mixed culture with staphylococci or streptococci from a severe case of suppurative hydroadenitis of nineteen years' duration. At the time this patient was seen, multiple draining sinus tracts were present on the buttocks and many healed scars were seen on the face, in the axillas and over the chest and back.

\*We are indebted to Dr. L. Dienes and Dr. J. V. Meigs for permission to report this case.

*Bact. fragilis* was isolated in this laboratory from the eye and cervix of a patient with conjunctivitis and arthritis who was regarded as possibly suffering from Reiter's disease. These organisms were recovered from the eye in pure culture, but could not be isolated from samples of blood or fluid from an affected joint or from other cases of Reiter's disease. Gonococci were not demonstrable. Until the cause of this disease is known, the etiologic significance of *Bacteroides* cannot be established.

CASE 7. An 83-year-old man was admitted on August 7, 1942, with a complaint of aching pain in the left flank of 3 weeks' duration. A large, fluctuant mass was felt in the left upper quadrant of the abdomen. X-ray examination revealed renal calculi on the left. The temperature was 100°F., and the white-cell count 16,000. The urine contained large numbers of red and white cells. A large perinephric abscess was found at operation. About 1000 cc. of foul yellow pus was drained from the abscess, and the kidney was removed. The abscess had eroded into the wall of the splenic flexure of the large bowel but had not penetrated the mucosa. Following the operation, sulfadiazine (2 gm. a day) was given for 10 days. A fecal fistula developed, but the patient did well and ran an essentially afebrile course. He was discharged 2 months after admission. The fistula closed within 5 months.

Bacteriology. Pus from the kidney abscess inoculated into meat tubes yielded a pure culture of *Bact. funduliformis*. The organisms were extremely pleomorphic, forming filaments and large bodies and exhibiting L-type variation. This strain, designated as No. 132, has been extensively studied.<sup>8, 11</sup>

#### BACTERIOLOGIC OBSERVATIONS

A great many species names have been given to the numerous strains of *Bacteroides* isolated in the last fifty years. The classification proposed by Weinberg et al.<sup>5</sup> affords an instructive outline of the situation. The more recent classification of Prévot<sup>41</sup> appears to possess certain fundamental merit in its broader aspects, but much more study is needed before any conclusion can be reached concerning which strains are true species and which are merely varieties.

Substantial progress has been made in Rettger's laboratory, where seventy-three strains of *Bacteroides* were found to fall into four serologic groups.<sup>35</sup> Later, two groups were recognized, chiefly on the basis of whether the strains were pleomorphic or nonpleomorphic.<sup>42</sup> Henthorne, Thompson and Beaver<sup>25</sup> found that six pleomorphic strains fell into one serologic group, whereas three nonpleomorphic strains fell into another. We have adopted the convention of placing pleomorphic strains in a *Bact. funduliformis* group and nonpleomorphic strains in a *Bact. fragilis* group. The latter corresponds to the *Bact. vulgatus* group of Lewis and Rettger.<sup>42</sup> The name "*fragilis*" is preferred because of its general use in the literature dealing with strains from infectious processes. This simple separation into two groups is obviously a temporary expedient, but it seems to have some clinical merit, since the septicemias due to pleomorphic strains appear to be severer than those due to nonpleomorphic strains.

Following is a résumé of data on strains recovered in this laboratory.

Meat tubes sealed with paraffin and Brewer's thioglycollate broth<sup>43</sup> proved to be satisfactory liquid mediums. For primary isolation, these mediums are enriched with 30 per cent ascitic fluid, to obtain growth within twenty-four to forty-eight hours. In an unenriched medium, growth may not appear until after a week or more.

Both pleomorphic and nonpleomorphic strains grow diffusely, with occasional exceptions in each group. Pleomorphic strains produce large, round bodies in abundance and often chains and filaments. Gas production is vigorous, and the cultures have a foul smell. Nonpleomorphic strains grow as uniform, small bacilli, produce less gas and have a less marked odor.

Anaerobiosis for plate cultures was obtained by the Fortner method.<sup>44</sup> After forty-eight hours' incubation, colonies on ascitic agar plates average 1 mm. in diameter. On blood-agar plates they are smaller. The colonies are smooth, white or gray, convex with an entire edge and nonhemolytic. Some pleomorphic strains produce yellow colonies and may exhibit beta hemolysis inconsistently. Of seven pleomorphic strains, three produced pleuropneumonia-like colonies as variant growth forms (L-type variation). Both L-type colonies and regular bacilli were seen to develop from the large bodies, which are so frequent in these strains and which were shown to contain a nuclear apparatus.<sup>9, 12</sup>

Of three pleomorphic strains tested, all produced hydrogen sulfide and one produced indol. Of four nonpleomorphic strains tested, two produced small amounts of hydrogen sulfide and none produced indol. Heat-resistance tests made with three pleomorphic and two nonpleomorphic strains showed that the organisms did not survive a temperature of 60°C. for twenty minutes. A nonpleomorphic strain from a case of meningitis produced large capsules. Motile organisms were never seen, nor were spores. The large bodies cannot be regarded as spores, since they are not heat-resistant and do not have the highly refractile quality characteristic of spores. All strains were gram-negative and strictly anaerobic.

Cultures of three pleomorphic strains injected subcutaneously into guinea pigs and rabbits produced only local abscesses. Intravenous injection of rabbits occasionally resulted in death with multiple abscesses or accompanied by cachexia with no localized lesions. Mice two weeks old injected intraperitoneally with one strain died within forty-eight hours with diffuse peritonitis. Old mice were not susceptible.

#### DISCUSSION

*Bacteroides* are natural inhabitants of mucous membranes, from which sites they may invade the tissues, blood or body cavities. They give rise to, or participate in, a great variety of pathologic processes. That *Bacteroides* infections are by no means rare is attested by the observation of 20 cases in this hospital within four years. The types of infection can be classified as follows: septicemia arising from throat infections, otitis media, surgery or infections of the large bowel, surgery or infections of the genitourinary tract or gunshot wounds; meningitis arising from chronic otitis media; peritonitis arising from appendicitis or leakage from colon (a mixed infection) or from salpingitis; infections of mucous membranes, including tonsillitis, otitis media, chronic cervicitis, and chronic prostatitis; and abscesses of the tonsils, liver, lungs, joints, brain, kidneys, Bartholin's glands, periurethral glands and skin.

The most frequent severe *Bacteroides* infections are septicemias arising from throat infections or following operations on the large bowel and meningitides arising from chronic otitis media. A case of *Bacteroides* peritonitis arising from salpingitis

and clinically simulating gonococcal peritonitis is noteworthy. The occurrence of *Bacteroides* septicemias in epidemic form in a group of soldiers with gunshot wounds, as described by Bogdán,<sup>26</sup> is of unusual interest. Although most *Bacteroides* infections appear to arise from organisms that are part of the normal body flora, this epidemic suggests that in some cases implantation of particularly virulent strains is a factor, and indicates the desirability of isolating recognized cases occurring in hospitals containing wounded men.

It is curious that *Bacteroides* and infections produced by them are not mentioned in some outstanding clinical and bacteriologic textbooks. This neglect is probably due to the fact that these organisms are easily missed in routine bacteriologic study, since they are anaerobic, tend to grow slowly and often require the presence of serum or ascitic fluid in the medium. It is hoped that this paper will stimulate more careful search for these organisms.

### SUMMARY

A review of *Bacteroides* infections based on cases collected from the literature and on those seen at the Massachusetts General Hospital is presented. The types of infections in which *Bacteroides* should be suspected are described. Methods for the cultivation and classification of the organisms are discussed.

Treatment consists chiefly of surgical and supportive measures. Animal experiments indicate that sulfonamides may be of value, but there is as yet no conclusive clinical evidence to this effect.

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## ALKALOSIS DURING SULFADIAZINE THERAPY FOR PNEUMOCOCCAL MENINGITIS\*

## Report of a Case

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**M**ENINGITIS due to a pneumococcus has a high mortality.<sup>1</sup> When complicated by diabetes and poor kidney function, it becomes a problem in therapy, as illustrated by the following case.

A 61-year-old, Italian housewife entered the Rhode Island Hospital on March 13, 1944, in a comatose state with a 4-day history of headache, backache, epigastric pain and vomiting. She had become drowsy 12 hours before admission and had gradually lapsed into coma.

Physical examination revealed a comatose woman breathing noisily and heavily through the mouth. The skin was clear. The eyes deviated to the left. The pupils were equal. The ears were normal. The neck was rigid. The lungs, heart and abdomen were not remarkable. The blood pressure was 180/90. The temperature by mouth was 104.2°F. The extremities showed no edema or varicosities. Bilateral Kernig signs were elicited. The patella and biceps reflexes were normal.

On admission the patient was suspected of having meningitis. A lumbar puncture yielded cloudy fluid under 370 mm. of pressure containing Type 3 pneumococci. The blood-sugar level was 680 mg. per 100 cc. and the carbon dioxide combining power 33 vols. per cent. The blood urea nitrogen was 26 mg. per 100 cc., and the creatinine 3.2 mg. The blood culture developed Type 3 pneumococcus. A blood Hinton reaction was positive. The urine showed a +++ test for sugar, a ++ test for albumin, a specific gravity of 1.022 and a positive test for acetone. The sediment contained many red and white cells and numerous granular casts. The white-cell count was 27,800, with 93 per cent polymorphonuclear leukocytes and 7 per cent lymphocytes. The red-cell count was 3,900,000, and the hemoglobin 15.1 gm.

Within the first 2 hours of admission, the patient was started on 5 gm. of sulfadiazine intravenously and was given 100,000 units of Type 3 antipneumococcus serum by the same route (Fig. 1). She was given 50 units of regular insulin and 50 units of protamine-zinc insulin subcutaneously and also 50 units of regular insulin in normal saline solution parenterally. Twelve hours later, she was started on a pre-coma regime consisting of 5 units of regular insulin for each "+" of sugar in the urine. She received 2 gm. of sulfadiazine intravenously every 8 hours. The total parenteral fluid therapy during the first day totaled 2000 cc. of normal saline solution and 2000 cc. of 5 per cent dextrose solution. The patient was still in coma the following day. The urinary output was extremely low. The sediment continued to show many red and white cells and a ++ test for albumin. The blood-sugar level had dropped to 362 mg. per 100 cc. Fifty thousand more units of antiserum was given.

On the 3rd hospital day, the patient responded to treatment and began to take sodium bicarbonate (1 heaping teaspoonful in water every 2 hours, alternating with and without sulfadiazine). The blood culture was sterile. X-ray films of the chest showed no abnormalities. The blood urea nitrogen had risen to 41 mg. per 100 cc., and the creatinine to 3.3 mg. The blood-sulfadiazine level was 18.8 mg. per 100 cc. of free drug and 22.6 mg. of total drug. The urinary sediment still contained numerous red and white cells and albumin.

On the 4th day, the blood urea nitrogen was 54 mg. per 100 cc., and the blood-sulfadiazine level 20.2 mg. of free and 28.6 mg. of total drug. On the 5th day, the temperature was almost normal, and the patient was subjectively and objectively much better. The blood urea nitrogen was 56 mg. per 100 cc., the creatinine 5 mg., and the sugar 414 mg.

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Sodium bicarbonate was continued as previously noted. On the 6th day, diarrhea and distention were noted. Sodium bicarbonate was given only once every 4 hours. Kaopectate and paregoric were administered. On the 7th day, the patient was well enough to take a liquid diet. She was still receiving parenteral fluids. On the following day, however, she became less responsive and had a convulsive seizure. The eyes deviated to the left, and there was spasm of the right side of the face and spasticity of the entire body. After the seizure, twitching of various muscles of the body was noted, particularly those of the face and upper extremities.

From the 3rd to the 8th day, the patient received 345 gm. of sodium bicarbonate by mouth. The total fluid intake by all routes in this period amounted to 17,600 cc., and the total urinary output was 5020 cc.

On the 8th day, the carbon dioxide combining power was 110 vols. per cent, compared with 33 vols. 7 days previously. The whole-blood chloride level, expressed as sodium chloride, was 292 mg. per 100 cc., and the blood-sulfadiazine level 14.2 mg. of free and 25.1 mg. of total drug. The Chvostek sign was markedly positive, and the patient was having periods of apnea, followed by rapid breathing. She was stuporous, but responded to vigorous shaking and took fluids by mouth. She was given calcium chloride by vein and ammonium chloride by mouth. The convulsive seizures stopped, but the twitching of various muscles continued. An attempt was made to increase the chlorides by intravenous normal saline solution, since the patient had improved only slightly after 24 hours' treatment with 18.5 gm. of ammonium chloride and 3 gm. of calcium chloride. Breathing of 10 per cent carbon dioxide and 90 per cent oxygen was attempted to relieve the apneic phases, but this had only a temporary effect. Ten cubic centimeters of 0.07 per cent hydrochloric acid and 5 cc. of 0.5 per cent hydrochloric acid were administered intravenously, but no more was given for fear of further damaging the kidneys by formation of acid hematin. The patient was becoming edematous. Abdominal distention due to gas was marked.

In one day the carbon dioxide combining power was brought down to only 104 vols. per cent. The sodium chloride had risen to 330 mg., the blood urea nitrogen was 50 mg. per 100 cc., and the creatinine 5.1 mg.

On the 10th day, after one more day of treatment of the alkalosis with 2 gm. of calcium chloride intravenously and 6 gm. of ammonium chloride by mouth, the carbon dioxide combining power was down to 86 vols. per cent and the sodium chloride up to 378 mg. The blood urea nitrogen was 50 mg., and the creatinine 6 mg. per 100 cc. The patient looked much better, but the urinary output was decreasing.

On the 11th day, because the kidney output was only 400 cc., ureteral catheterization was done. Sulfadiazine was stopped because the patient had run a near-normal temperature for several days and because it was suspected that kidney shutdown might have been due to the drug. Insulin was also stopped, because with the decrease in infection the severity of the diabetes decreased. The blood urea nitrogen had risen to 62 mg. and the creatinine to 6.5 mg.; the carbon dioxide combining power had dropped to 75 vols. per cent, and the sodium chloride to 332 mg.

On the 12th day, the kidney output was less than 100 cc. Tissue edema was marked. The urine was small in amount and was grossly bloody and full of sediment.

On the 15th day, after persistent continued treatment with intravenous solutions, the kidneys were excreting large amounts of urine. Because the total protein was 3.7 gm. per 100 cc., 500 cc. of blood plasma was given in an attempt to relieve the edema. The creatinine was 8.8 mg., the blood urea nitrogen 96 mg., and the sodium chloride 340 mg. per 100 cc. On the 17th day, the urinary output continued high. Edema had decreased considerably. The patient felt well and was put on a liquid diet. A lumbar puncture yielded spinal fluid with an initial pressure of 350 mm., a protein of



28 mg. per 100 cc. and 1 polymorphonuclear and 10 lymphocytic cells per cubic millimeter. The blood urea nitrogen and creatinine levels were dropping, and the carbon dioxide combining power was 62 vols. per cent. Two days later the patient became comatose. No cause was found, although

The patient was started on penicillin, being given 15,000 units intramuscularly every 3 hours. The response both clinically and subjectively was excellent. The temperature dropped to normal. In 3 days she received 195,000 Oxford units of penicillin, and recovery from the pneumonia and

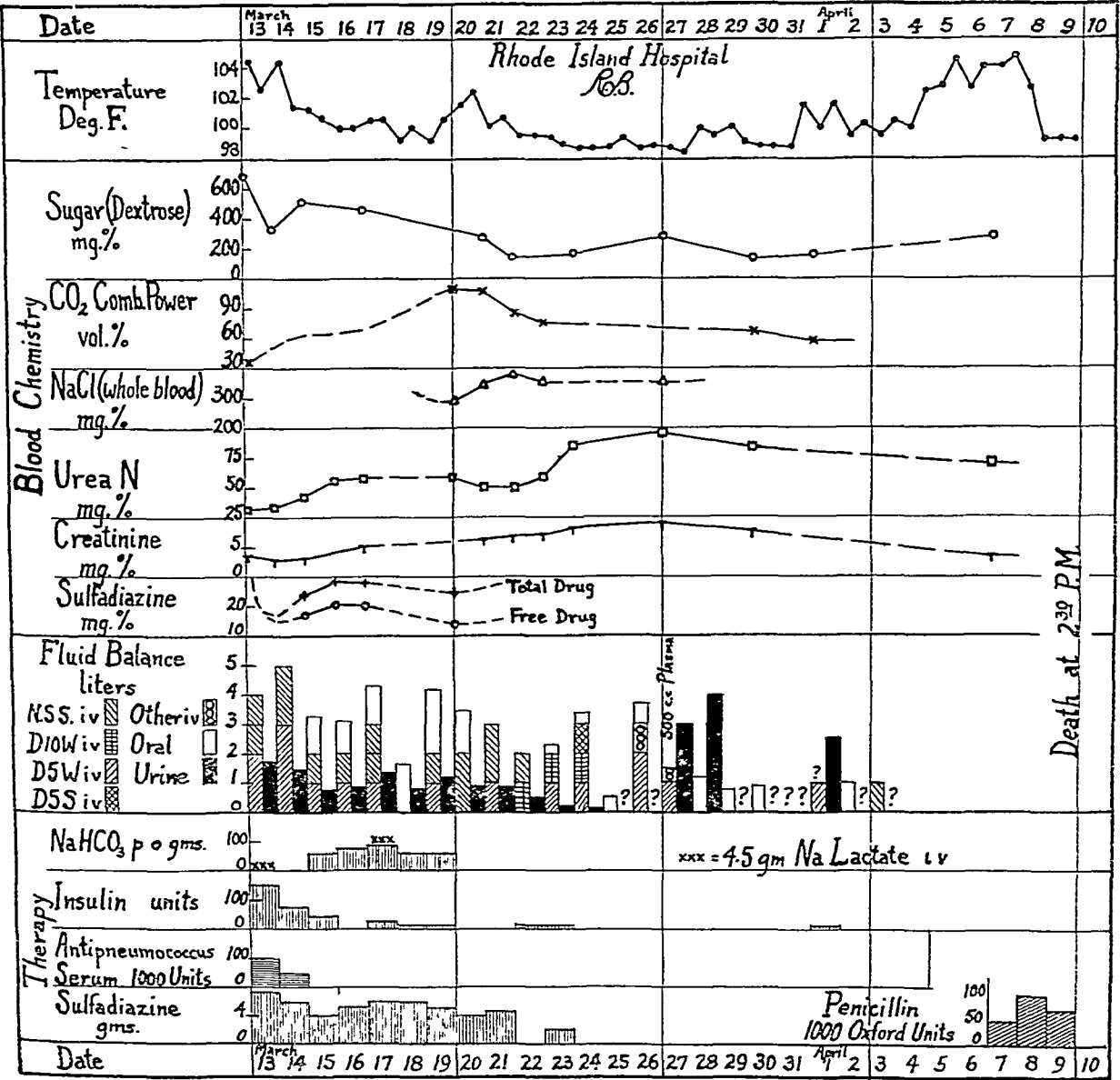


FIGURE 1.

cerebral thrombosis was suspected. She came out of coma without treatment in 6 hours. On the 24th day, the patient developed a temperature of 103.5°F. Lobar pneumonia was diagnosed clinically. X-ray examination showed consolidation in the chest. A lumbar puncture yielded clear spinal fluid with 95 mg. of protein per 100 cc., 45 polymorphonuclear cells and 25 lymphocytes per cubic millimeter, a positive Hinton reaction and a gold-sol curve of 5554321000. On the 26th day, blood and urine cultures were reported as positive for a coagulase-positive *Staphylococcus aureus*. The blood urea nitrogen was 48 mg., the creatinine 3.3 mg., and the blood sugar 268 mg. The white-cell count was 12,700.

septicemia appeared probable when the patient suddenly had a convulsive seizure lasting 5 minutes and died. Permission for autopsy was refused.

DISCUSSION

On admission, the carbon dioxide combining power of 33 vols. per cent and a positive test for acetone in the urine indicated that diabetes mellitus was a contributing, but not the major, factor in producing unconsciousness. The need for insulin, in



this previously unknown diabetic patient, decreased as the infection was controlled. She had poor kidney function, as shown by the urine sediment and albumin, a specific gravity of 1.022 in the presence of both albumin and sugar, and nitrogen retention that increased after adequate hydration. The dosage of sulfadiazine was not high, but excretion was poor. This is shown by the high values for free drug and by an amount of acetylated drug in the blood about ten times the usual one.

Sodium bicarbonate was given by mouth to aid in excretion of the sulfadiazine. In pneumonia patients we have given up to 60 gm. a day, but still find in some cases a urine with a pH less than 7. This patient was given 345 gm. in a period of five days, with the resulting coma and convulsions of alkalosis. The kidney insufficiency undoubtedly contributed to the alkalosis by failure of acid-base regulation. In subjects with normal kidneys, Thompson, Mitchell and Kolb<sup>2</sup> were able to give daily doses of 60, 75 and 130 gm. of sodium bicarbonate in a three-day period, respectively, without the development of alkalosis and with a rise in the carbon dioxide combining power only to 68 vols. per cent. Jeghers and Lerner<sup>3</sup> believe that 8 per cent of cases of peptic ulcer treated with alkalis containing sodium bicarbonate develop alkalosis, although the syndrome is seldom recognized.

The reaction of the urine on the second and third hospital days was pH 5.0. On the fourth and fifth days it was pH 8.0, and on the ninth day, after one day of acid therapy, it was pH 7.0. Usually an alkaline urine is excreted when the carbon dioxide combining power is 75 vols. per cent or more.

Other signs accompanying the development of alkalosis were edema, coma, apnea, a positive Chvostek sign and convulsions. Excess alkali causes the tissue proteins to hold more water and the interstitial fluid increases, especially when a low plasma protein is present. Coma with apnea alternating with hyperpnea is found in severe alkalosis. During the compensated phase, carbon dioxide accumulates as carbonic acid in the plasma, but when the sodium bicarbonate (carbon dioxide combining power) rises higher, the pH of the plasma shifts to higher values and coma begins. The relative alkalinity inhibits the response of the respiratory center to carbon dioxide, and periods of apnea followed by deep respiration may result. It also decreases the ionization of calcium compounds in the plasma, although there is no decrease in total calcium. With less than normal calcium ions neuromuscular irritability is increased, so that the Chvostek sign is positive, and with marked changes, convulsions may begin.

Calcium chloride is useful for emergency treatment, since for an hour or two it supplies extra calcium ions, and it also has a slight acidification action. Ammonium chloride is a better agent, since the cation is converted to urea by the liver and

some bicarbonate is replaced by chloride. The giving of intravenous hydrochloric acid is a rather direct attack on the alkalosis, since its reaction with bicarbonate forms carbon dioxide, which is excreted by the lungs, and sodium chloride. Treatment with intravenous sodium chloride solution depends on the ability of the kidney to excrete sodium bicarbonate and retain sodium chloride.

Treatment of this case with all these agents improved the alkalosis, as shown by a fall in carbon dioxide combining power, and with this there was a rise in the sodium chloride level of the blood. It was impossible to show a return to normal of blood chloride, probably because of rapid diffusion of the parenteral sodium chloride into the tissues and because of nitrogen retention, which, by phosphate and sulfate retention, left less blood base to exist as chloride. The blood sodium chloride of 292 mg. per 100 cc., found when the patient was in alkalosis, developed in spite of the giving of 9000 cc. of 0.85 sodium chloride solution during the previous seven days.

Sulfadiazine was continued for three days after the alkalosis episode. After it was stopped on the eleventh day because of a fall in urinary output, the nitrogen constituents of the blood rose for four days. The small amounts of urine voided contained blood and a crystalline sediment. Apparently the sodium chloride used to treat the alkalosis had caused a migration of fluids into tissue spaces, and sulfadiazine crystals in the kidney tubules had produced almost complete anuria. The kidneys recommenced excretion after the use of intravenous 5 and 10 per cent dextrose solutions in distilled water, and with increased urine output, the blood urea nitrogen and creatinine levels rose.

This patient had been comatose on four occasions while in the hospital. Coma on admission was most likely due to the meningitis together with diabetes. Coma on the eighth day was probably caused by alkalosis. There were two unexplained comas, one on the twentieth day and the other just preceding the convulsions and death. Although the positive blood and spinal-fluid Hinton reaction, a paretic colloidal-gold curve and increased total protein and cell count of the spinal fluid were consistent with neurosyphilis, this diagnosis was relegated to the background owing to the severer and more obvious infections present during the illness. It is unlikely that meningovascular syphilis was a contributing factor in this patient's death. Localized abscesses are found complicating pneumococcal meningitis. That this was the cause of death is not so likely. There were no progressive symptoms indicating increase in intracranial pressure, nor was the initial pressure on the last tap elevated. Other possible causes of death are a cerebral hemorrhage on a hypertensive basis, acute staphylococcal endocarditis with ruptured aortic cusp and resulting lodgment of an embolus in the cerebral artery, and an acute myocardial failure from the severe

and long illness. The last seems the most probable cause.

### CONCLUSIONS

The administration of sulfadiazine and specific antipneumococcus serum helps to sterilize the blood stream and spinal fluid in cases of Type 3 infection.

A damaged kidney not only excretes sulfadiazine poorly but may cause alkalosis if sodium bicarbonate is given in considerable dosage with the sulfonamide. Careful observations of the blood urea nitrogen and blood-sulfonamide levels, the carbon dioxide combining power and the fluid balance are necessary in cases in which kidney function is abnormal.

Treatment of an alkalosis may cause renal shut-down when large amounts of sulfadiazine are present in the body.

Apparent sterilization of blood and spinal fluid from Type 3 pneumococci with specific antipneumococcus serum and sulfadiazine, apparent recovery from alkalosis and apparent sterilization of blood from *Staph. aureus* with penicillin were insufficient to save this patient's life.

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## CLINICAL NOTE

### CUTANEOUS HORN

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**P**ATIENTS with pronounced cutaneous horns are so rarely seen that the following case appears worthy of recording.

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An 88-year-old man was admitted to the New Hampshire State Hospital with a horny growth on the back of the right hand (Fig. 1). It was about 15 cm. long, curving distally in a semicircle from the area of origin over the first and second metacarpophalangeal joints to the middle phalanx of the ring finger. It was apparently a hyperkeratosis. A relative stated that the growth started as a wart 10 years previously, and that the patient used to trim it with a razor blade. Gradually the tissue became hard and he filed or ground it down.

The growth was removed in toto and sent to the pathologist. According to the report, the specimen consisted of a



FIGURE 1.

horn 14.5 cm. long in the shape of the letter C. The diameter at the base was 4 cm., and that at the tip, which was blunt, was 1.3 cm. The horn was longitudinally striated. The color varied from light brown at the proximal end to dark brown at the tip. Microscopic examination of the tissue at the base revealed stratified squamous epithelium with long papillary processes, overlying fibrous connective tissue in which there were many lymphocytes. The stratum corneum was composed of innumerable layers. There was no evidence of malignant degeneration. The diagnosis was cutaneous horn.

The patient made an uneventful recovery from a skin graft, and is still in the hospital.

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## MEDICAL PROGRESS

### DISEASES OF THE NEWBORN\*

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THE relatively high death rates that still prevail during early infancy are the cause of much concern throughout the country. The infant mortality during the first year of life for the United States in 1941 was 45.3 deaths per 1000 live births.<sup>1</sup> Of these deaths 27.7, or 61 per cent, took place in the first month of life, while 18.1 or 29 per cent occurred in the first twenty-four hours of life.<sup>2,3</sup>

The federal government, through the Children's Bureau, has taken a leading role in attempts to lower the incidence of such deaths. The Children's Bureau has encouraged state health departments to develop plans to improve the care of premature infants, and at least forty-three states have presented such a program.<sup>4</sup> The Bureau, with the co-operation of various nationally recognized pediatric organizations, has prepared and published *Standards for the Care of Newborn Infants*. This authoritative pamphlet can be obtained by writing the Children's Bureau and should be studied by every hospital attempting the care of such infants. The Children's Bureau has also developed and published a booklet entitled *Plans for Hospital Nurseries*, which was drawn up with a view to protect the infants from infection and to facilitate the work of physicians and nurses.<sup>4</sup> In addition, as a wartime measure, the Bureau has been given the responsibility of administering the Emergency Maternal and Infant Care (EMIC) Program for the wives and infants of enlisted men.

#### PREMATURITY

The ideal method of decreasing the number of deaths from prematurity would be to prevent the premature onset of labor; up to the present time, however, no one has succeeded in doing this except in a few isolated cases. It is therefore necessary to improve the environment into which the premature infant is born if its chances of survival are to be increased.<sup>5</sup>

Although a premature infant may suffer and die from any of the pathologic conditions affecting an infant born at term, there are many who fail to show pathologic lesions that can be discovered by known chemical or histologic means. The immediate reason why the majority of otherwise normal premature infants die is inability to absorb oxygen through the inadequately developed lung. As the fetus grows, capillaries gradually branch out from

the septal vessels and push their way between the cuboidal alveolar cells, thrusting them aside so the capillaries lie uncovered in direct contact with the air spaces. If the capillaries in contact with the air and capable of receiving oxygen are too small to support life, the infant cannot survive. An effective method of oxygen therapy increases the percentage of oxygen in the inspired air and thus allows greater absorption.<sup>6</sup> Many small premature infants have survived in an atmosphere containing 50 per cent oxygen for several months or until they have developed sufficiently to live under normal atmospheric conditions.<sup>6</sup>

Stevenson has made an important clinical application of the use of carbonic anhydrase in disease of the newborn.<sup>7</sup> The action of this biologic catalyst is to expedite the liberation of carbon dioxide from carbonic acid. Without its influence this gas cannot be unloaded from the blood at a speed commensurate with the rate of pulmonary circulation. This delay indirectly impedes the uptake of oxygen, for which reason oxygen therapy is of no avail. Stevenson found that the concentration of circulating carbonic anhydrase is low in the newborn, and even lower in the premature infant. It is likely to be especially low in such infants as are cyanotic without obvious reason. The mortality rate in these cases is high, but post-mortem examination reveals little cause of death. Certainly, the older notion of congenital atelectasis is fallacious in such cases. When, however, these infants are transfused, their blood enzymes become rapidly elevated and their cyanosis disappears; furthermore, the mortality rate is considerably lowered.

*Feeding and energy requirements.* Gordon<sup>8</sup> states that the caloric intake of premature infants during the first few days of life is a matter of no real concern. Even though the caloric intake is zero the total negative energy balance is small since the basal metabolism is only 40 to 50 calories per kilogram per day and the quotas for fecal loss and specific dynamic action, which depends on the food intake, are small. For older premature infants the basal metabolic rate in terms of body weight averaged 58 calories per kilogram per day. The only change in the number of calories per kilogram from week to week was an increase of 5.3 calories from the first to the second week of postnatal life.<sup>9</sup>

The total caloric requirement of premature infants is from 75 to 90 calories per kilogram per day for the first two or three weeks of life, and thereafter 100 to 125 calories.<sup>10,11</sup>

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The premature infants have the power to metabolize carbohydrate as efficiently as do full-term infants.<sup>9</sup> They also have an ability to absorb protein equal to that observed in full-term infants.<sup>11</sup> Many premature infants exhibit a defect in their alimentary absorption of fat, irrespective of the type of fat, but inability of the alimentary tract to split fat is not the determining factor in this defective absorption. Whether the defect in the transport of fat across the intestinal wall is dependent on an anatomic underdevelopment of the capillaries and villi, or a functional impairment of the enzyme mechanisms concerned with phosphorylation of fat or on differences of intestinal motility is a problem reserved for future study. Whatever the mechanism involved, Levine and Gordon<sup>12</sup> are convinced that the failure of some premature infants to thrive on presumably adequate diets may be the result of faulty absorption of ingested fat. These authors recommend a reduced fat content in the diet for premature infants and the maintenance of the total dietary calories at the same level by replacement with protein and carbohydrate. Their feeding mixture contains 120 calories per kilogram of body weight, and the total fluid volume is 150 cc. per kilogram, the basic constituents being 2.5 gm. of fat, 18 gm. of carbohydrate and 6 gm. of protein per kilogram.

Levine and Gordon<sup>11</sup> question the assumption that human milk is the ideal food for premature infants. They point out that it is a relatively dilute feeding and it may predispose to increased peristalsis and diarrhea, abdominal distention and respiratory embarrassment. It is relatively high in fat. It is low in mineral content, particularly in calcium and phosphorus, and there is abundant evidence to prove that, even though all the calcium and phosphorus contained in the daily amounts of human milk ordinarily ingested by the premature infant are completely absorbed and utilized, the amounts are still insufficient to meet the demands for bone growth during the first year, as determined by chemical analysis of the bones of fetuses and by studies of mineral retention.<sup>13</sup> Human milk is relatively low in protein, and it has been shown that augmentation of the protein intake is accompanied by an increased alimentary absorption of the protein ingested. The rapid rate of body growth of premature infants implies the desirability of a correspondingly high protein intake for the manufacture of the needed extra protoplasm.

There are certain arguments in favor of human milk as the ideal food for premature infants. Teleologically, a food supplied by nature is preferable to any form of artificial food. There is suggestive, but not conclusive, evidence that immune substances may be transferred in the breast milk and particularly in the colostrum. Nursing at the breast has many practical and economic advantages. The physiologic and psychologic benefits to the mother

of suckling her infant at the breast cannot be gainsaid. Finally, human milk has a low content of electrolytes and the renal excretion of such substances may be better handled in this form by the premature infant, whose kidneys have been shown to be less efficient excretory organs than those of full-term infants.<sup>11</sup>

Regarding the relative merits of human and cow's milk as the ideal food for premature infants Levine and Gordon<sup>11</sup> suggest that in hospital practice or when human milk is not available except at great expense a cow's milk mixture low in fat is an adequate substitute.

*Fluid requirements.* Levine and Gordon<sup>11</sup> recommend the routine use of relatively low fluid intakes—130 to 150 cc. per kilogram of body weight—in the feeding of premature infants. When fluid intake was below 95 cc. per kilogram large amounts of water were withdrawn from the body, resulting in a negative water balance and dehydration. With higher fluid intakes the infants retained in their bodies a relatively fixed amount and merely eliminated the extra water as extra urine.

*Vitamins.* The tendency of the premature infant to have hemorrhagic manifestations of a serious nature is explained by the fragility of his capillaries and the low prothrombin content of his blood plasma. The paucity of vascular elastic tissue, the frequent occurrence of anoxia with its deleterious effect on capillary integrity and the low body reserves of vitamin C required for building so-called "cementing substances" are probably the chief factors contributing to the increased permeability of the capillaries of the premature infant.

Levine, Marples and Gordon<sup>14</sup> have recently demonstrated the important role of vitamin C in the intermediary metabolism of protein in premature infants. The action of vitamin C is specific in completing the oxidation of two aromatic amino acids, phenylalanine and tyrosine. A defect in aromatic-amino acid metabolism can be produced at will in premature infants by feeding mixtures of cows' milk containing 5 gm. or more of milk protein per kilogram of body weight and by withholding vitamin C. The defect can be promptly eradicated by the administration of vitamin C in adequate dosage. The authors therefore recommend that all premature infants be given 25 to 50 mg. of ascorbic acid daily from birth and from 75 to 100 mg. daily after feedings of cows' milk have been instituted.

A reduced antenatal storage of calcium, phosphorus and possibly vitamin D predisposes the premature infant to rickets. Added to this predisposition is the defect in fat absorption and presumably in the fat-soluble vitamins, as well as the rapid rate of body growth and the increased demands for retention of calcium and phosphorus, often in the face of a diminished dietary supply provided in human milk. Even if vitamin D is administered and absorbed in adequate amounts, its efficacy in

promoting renal tubular reabsorption of phosphate, which Harrison<sup>15</sup> has demonstrated to be one of the functions of this vitamin in older subjects, may be minimal as a result of the defect in renal function. This impairment, together with faulty alimentary absorption of vitamin D, may explain the high dosage of the vitamin needed to prevent rickets in premature infants.

#### MISCELLANEOUS CONGENITAL DEFECTS

Warkany<sup>16</sup> has submitted further proof to defend his thesis that certain types of maternal nutritional deficiency can result in specific malformations in the young. The offspring of female rats reared and bred on a diet deficient in the vitamin factor found in pigs' liver produced 32 per cent abnormal offspring. The addition of 2 per cent dried pig liver to the diet prior to the fourteenth day after mating prevented the occurrence of deformities. The defects occurred in the skeletal system and included shortness of the mandible, shortness or absence of the radius, ulna, tibia or fibula and fusion of the ribs and of the sternal centers of ossification. In another experiment Warkany<sup>17</sup> observed congenital skeletal malformations in 45 per cent of the offspring of female rats fed a rachitogenic diet. The changes observed comprised a pronounced curving of the radius, ulna, tibia and fibula, as well as angulation of the ribs, and were quite distinct from those seen in the vitamin B deficient diet. The addition of vitamin D to the maternal diet prevented these malformations. In his most recent communication Warkany<sup>18</sup> describes marked maldevelopment of the eye in the offspring of female rats fed a diet deficient in vitamin A.

New light has recently been thrown on the etiology factors involved in certain congenital malformations by three series of cases reported from Australia in which virus infections, particularly German measles, occurring early in pregnancy seem to be definitely related to congenital defects.<sup>19</sup> Gregg reported a series of 78 patients with congenital cataract, 44 of whom also had congenital heart disease, occurring in infants whose mothers, with few exceptions, had suffered from what was presumed to be German measles in the early months of pregnancy. Swan reported 49 cases of rubella occurring in all stages of pregnancy, of which 25 occurred in the first two months, every one of which showed congenital defects, usually of the eye or heart. In 50 per cent of those having rubella in the third month the infants showed defects. The congenital malformations encountered were 17 heart lesions, 14 defects of the eye, 7 deaf mutes, 1 mongoloid idiot and several cases each of microcephaly, hypospadias and mental retardation. In a follow-up communication Swan added 10 more cases of congenital malformations occurring in infants born of mothers who had had rubella early in pregnancy. Reese reported 3 cases. Erickson<sup>19</sup> added 11 cases

of congenital cataract and congenital heart disease occurring under similar conditions in this country.

Both Swan and Erickson raise the question whether therapeutic abortion is justified if rubella occurs during the first two months of pregnancy, since in the experience of both, 100 per cent of such babies had serious congenital malformations.

#### ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULAS

Esophageal atresia and tracheoesophageal fistulas have formerly been considered incompatible with life. In the last few years, however, a few successes or partial successes have been reported from various parts of the country and it now appears correct that surgical intervention should be attempted. Ladd<sup>20</sup> has recently reported 39 such patients operated on at the Children's Hospital, of whom 11 are living. He emphasizes that the surgical approach to combat this condition is subject to change but that, at the present time, primary anastomosis of the esophagus is the operation of choice when the two ends of the esophagus can be approximated without too much tension. In cases in which the ends of the esophagus are far apart, the three-stage operation, with the ultimate construction of an anterior thoracic esophagus, is a safer operation. The last 5 patients operated on according to this plan are living and doing well.

Ladd predicts that, if obstetricians and pediatricians are alert and make an early diagnosis, the mortality will be further lowered.

The diagnosis may be suspected when the newborn infant has an excess of mucus or saliva in the mouth, with or without an associated cyanosis. The next suggestive symptom is vomiting of mucus even though no food or fluid has been given, or vomiting after the first feeding. It is essential to a good prognosis, however, that the diagnosis be made before food is given, since its presence in the lung will probably result in a pneumonia. On the least suspicion, a stiff catheter should be passed down the esophagus in order to demonstrate a blind pouch. If in doubt x-ray films should be taken with the catheter in place. Barium should not be given, since its presence in the lung results in an inflammatory reaction; if an opaque medium is needed it is much safer to use lipiodol. The presence or absence of rales in the lungs and of air in the intestinal tract depends on the type of anomaly present.

#### SPINA BIFIDA AND CRANIUM BIFIDUM

Ingraham and Swan<sup>21</sup> have analyzed 546 infants and children seen at the Children's Hospital during the last twenty years to see whether there can be established any reasonably definite criteria for prognosis, for operative therapy and for operative technics. They also wished to discover if the general attitude of hopeless pessimism toward these cases should not be modified by examination of the end

results. The authors found that 30 per cent of the patients with spina bifida and 34 per cent of those with encephalocele may expect a relatively normal life. They concluded that an unduly pessimistic prognosis is unwarranted until individual evaluation has been carefully pursued.

Ingraham and Scott<sup>22</sup> have also presented a series of 20 cases with the Arnold-Chiari malformation to emphasize that this is not a rare condition but is a frequent accompaniment of myelomeningocele. This malformation is a congenital anomaly of the hind brain characterized by a downward elongation of the cerebellum and brain stem into the cervical portion of the bony spinal canal. Surgical treatment should be limited to patients without extensive paralysis of the lower extremities and sphincters. It should not be offered if hydrocephalus is so advanced that it is inconsistent with normal mental development. The authors believe that encephalography may help in identifying the associated microgyria, which is probably another contraindication to operation.

#### CONGENITAL CEREBRAL PALSY

Until twenty-five years ago Little's disease or congenital cerebral palsy was held to be the result of various factors, chiefly birth trauma, acting during birth on the central nervous system. Of late, doubt concerning the prime etiologic role of birth trauma has arisen because of post-mortem examinations that failed to show any evidence of birth trauma and because there was a high incidence of essentially normal birth histories in these cases. Yannet<sup>23</sup> analyzed 86 patients in whom the diagnosis of congenital cerebral palsy had been made and uncovered data showing the major importance of developmental cerebral defects in the etiology, as well as information on certain genetic relations. Yannet found the average age of the mothers at the time of birth of the affected child was significantly greater than that of child-bearing women in the general population. The affected children tended to have a later ordinal birth rank than would be normally expected. There was a significant incidence of similarly affected siblings of patients with cerebral palsy. The incidence of mental deficiency in the nonaffected siblings was greater than would be expected from random selection. Finally, there was an unusually high incidence of associated physical defects, especially those involving the eyes.

#### ERYTHROBLASTOSIS FETALIS

The pathogenesis of erythroblastosis fetalitis has been established in great measure through the brilliant work of Philip Levine, who has recently published an excellent review of the subject.<sup>24</sup> Erythroblastosis fetalitis is caused by isoimmunization of the mother by a dominant hereditary blood factor in the fetus, most frequently the Rh (rhesus) factor. This intrauterine hemolytic disease of the

fetus and the newborn infant occurs under highly specific conditions, determined by the presence or absence of the Rh factor in the parents. In more than 90 per cent of the cases the father's blood contains the Rh factor (Rh+), the mother's blood lacks the factor (Rh-) and the fetal blood possesses it (Rh+). The two essential steps in the pathogenesis of erythroblastosis fetalitis are the response of the Rh- mother to the Rh+ fetal blood by production of anti-Rh agglutinins and the continuous passage of maternal anti-Rh agglutinins through the placenta to react with and hemolyze the susceptible fetal Rh+ blood.

In 1940, Landsteiner and Wiener studied the specificity of an immune serum produced in rabbits and guinea pigs by injections of the blood of *Macacus rhesus*. This serum was found to agglutinate 85 per cent of all human bloods. These bloods were termed Rh+, and the 15 per cent inactive bloods, Rh-. The experimental anti-Rh serum produced by rabbits or guinea pigs cannot as yet be used as a routine diagnostic serum, since the resulting agglutinations are unreliable or difficult to read. For Rh typing one has had to depend, until recently, on high-titer human serum, which is found in only about 1 of 20 mothers of erythroblastotic infants. Since the Rh factor is a mosaic composed of several antigenic substances, not all the human anti-Rh serums in contrast to anti-A or anti-B testing serums, give parallel reactions.<sup>24</sup> There are, as a result, three main types of human anti-Rh serums: that agglutinating 87 per cent of random bloods and called "anti-Rh" by Wiener and Landsteiner; that agglutinating 85 per cent of random bloods, called "anti-Rh"; and that agglutinating 73 per cent of random bloods, called "anti-Rh<sub>1</sub>." It is therefore possible to have a small number of cases of proved erythroblastosis fetalitis in which evidence of isoimmunization (father Rh+ and mother Rh-) cannot be obtained provided that human serum of the anti-Rh<sub>1</sub> type is used.

The important problem of accurate Rh typing appears to be solved by the timely work of Diamond<sup>25</sup> at the Children's Hospital. Working in co-operation with the Department of Physical Chemistry of Harvard Medical School, he has been able to pool and concentrate low-titer anti-Rh serums, obtaining a globulin fraction that yields accurate typing results. Furthermore, the technic of typing is simple. It consists in mixing a drop of the concentrated anti-Rh serum with a drop of the unknown red-cell suspension on a glass slide and observing at once the presence or absence of agglutination.\*

\*The Blood Grouping Laboratory, 300 Longwood Avenue, Boston 15, is in need of more anti-Rh typing serum for the armed forces and civilian use. Physicians and hospitals are urged to send to the laboratory a few cubic centimeters of blood from any patient known to have had a baby with erythroblastosis delivered within the last two years. If the serum is found to contain a useful amount of anti-Rh agglutinins, the physician or hospital will be notified and requested to forward from 100 to 500 cc. of the patient's blood. Seventy per cent of the concentrated serum will be set aside for the military services and 30 per cent will be available immediately to the contributing physician or hospital in the form of standard anti-Rh typing serum.

The demonstration of Rh isoimmunization is possible in 90 per cent of the mothers of erythroblastotic infants, but in 10 per cent the mothers are Rh+ and some other cause for the syndrome must be found. Levine<sup>24</sup> suggests that there should be other blood factors besides the Rh factor capable of inducing isoimmunization. He was able to prove this point by demonstrating atypical agglutinins produced by two Rh+ mothers of erythroblastotic infants; both serums agglutinated all Rh- bloods but did not react with other Rh+ bloods. Since this new factor had some genetic relationship to the Rh factor, Levine suggested the two letters Rh be reversed, the terms "Hr" and "anti-Hr" being used to designate this new blood factor and its corresponding antibody. The Hr factor, however, can be held responsible for isoimmunization in only some of the Rh+ mothers. In a certain number of the remaining cases, isoimmunization may perhaps be induced by the factors A or B in fetal blood. In a few cases no cause for the isoimmunization could be demonstrated by present methods. It must be remembered that in some cases a clinical syndrome indistinguishable from erythroblastosis fetalis may be the result of fetal anoxia, syphilis or septicemia.

Potter<sup>26</sup> insists that, to diagnose erythroblastosis anemia, erythroblastemia and splenomegaly must be present. Other manifestations usually associated are edema, jaundice, hepatomegaly and placental hypertrophy. It is important to stress these diagnostic features, since the diagnosis of erythroblastosis fetalis is being made too widely and on insufficient evidence on the one hand and is still being overlooked on the other.

In approximately 12 per cent of all marriages the wife is Rh- and the husband is Rh+. If the father is homozygot, all the offspring will be Rh+; if he is heterozygot, there is a 50 per cent chance that the infant will be Rh-. Thus, in approximately 9 per cent of all births an infant with Rh+ blood is delivered of a mother with Rh- blood, but erythroblastosis actually occurs in only 0.1 to 0.2 per cent of all pregnancies. The Rh typing of all pregnant women is recommended, but as a result, 120 out of every 1000 couples may be upset, even terrified, at the possibility of a forthcoming erythroblastotic infant. In all fairness the reassuring fact that this is to be expected in less than 2 per cent of such matings should be emphasized. Furthermore, even should an erythroblastotic infant be found at delivery the ultimate outlook for over half of these patients is excellent.

The pathogenesis of this disease is still far from being completely solved. The Rh factor must play an important role, but one wonders why erythroblastosis fetalis occurs in only about 2 per cent of the Rh+ infants whose mothers have Rh- blood. It is obvious that there must be other unknown factors in the equation.

The termination of pregnancy by cesarean section as soon as the fetus becomes viable has been recommended in such cases, on the assumption that if the fetus can be delivered early enough in the course of pregnancy it may escape being affected by maternal agglutinins.<sup>26,27</sup> It has also been suggested that the mother's blood be watched closely for the appearance of agglutinins or for a rise in agglutinin titer and that the pregnancy be terminated at the time when agglutinins appear or when the titer suddenly rises.<sup>28</sup> If there were no hazard associated with prematurity, early delivery might be an advisable procedure on the supposition that the more prolonged the exposure to anti-Rh agglutinins, the more severe the disease. The fetus, however, is probably affected early in pregnancy, regardless of whether demonstrable agglutinins are present in the maternal circulation; furthermore, many infants become much more severely affected immediately after delivery than they were during intrauterine life. Too few cases have as yet been reported to indicate whether early delivery with the consequent discontinuation of direct exposure to anti-Rh agglutinins can outweigh the handicap of prematurity imposed on an infant already suffering from erythroblastosis. At the Chicago Lying-in Hospital, as well as in other clinics, infants have been delivered early by cesarean section only to die of erythroblastosis despite the administration of blood at birth, and it has been concluded that nothing is to be gained by premature delivery.<sup>26</sup>

In the obstetric management of the mother of a potentially erythroblastic infant it is unfortunate that there is no direct connection between the presence or absence of anti-Rh agglutinins in the maternal serum and the condition of the infant. Levine<sup>24</sup> failed to find anti-Rh agglutinins in more than 50 per cent of the mothers, although he quotes British workers as observing a higher incidence. He states that isoimmunization may occur even in the absence of demonstrable antibodies. Neither the presence or absence of anti-Rh agglutinins nor the titer of these agglutinins is a reliable index of the presence or severity of erythroblastosis in the infant.

The treatment of erythroblastosis fetalis is by transfusion of Rh- blood from a donor other than the mother.

#### INFECTION

In spite of increased knowledge regarding causes of infection in newborn infants and methods of prevention, epidemics still occur. Reports coming to the Children's Bureau indicate that they are increasing along with overcrowding of the maternity services. In a number of hospitals in different localities epidemics of diarrhea among newborn infants have been associated with mortality rates of from 30 to 50 per cent.<sup>2</sup> *Standards for Care of Newborn Infants and Plans for Hospital Nurseries*, two booklets issued

by the Children's Bureau and previously referred to, give valuable suggestions to assist in the prevention and control of all types of infection in the newborn.

Torrey and Reese<sup>29</sup> have found that the initial aerobic bacterial flora of the throat and nasopharynx of artificially fed newborn infants is largely acquired through direct contact with adults and not from the parturient canal. Droplets of saliva comprise the principal vehicle of transfer. The flora in premature infants is essentially the same as that in full-term infants of similar age. Although occasional contact with adult carriers of pneumococci, influenza bacilli and beta-hemolytic streptococci occurred, the first two organisms were not present and the streptococci were only rarely present in infants from one day to four weeks old.

These authors found that up to sixteen hours after birth the nasopharynxes and throats of 80 per cent of the infants exhibited sterility. Between twenty-four and forty-eight hours after birth 50 per cent of infants in wards exposed to ultraviolet irradiation still showed sterility, as contrasted with only 12 per cent of infants in wards not so exposed. Beyond that time results for the two groups were essentially alike, except in regard to hemolytic strains of *Staphylococcus aureus*. Ultraviolet irradiation did not retard the acquisition of nonhemolytic streptococci but did delay the presence of hemolytic strains of *Staph. aureus*; in the absence of ultraviolet irradiation an occasional air-borne transfer of the latter organism probably occurred.

Torrey and Reese conclude that ultraviolet irradiation does not prevent person-to-person transmission of pathogens through the air within the range of a few feet. Among infants from seven to twenty-five days old in wards without irradiation, 60 per cent were carriers of hemolytic strains of *Staph. aureus* in the nasopharynx, of which 86 per cent were coagulase positive and potential pathogens.

These workers also found that the strains of streptococci and of *Staph. aureus* normally present in the throats and nasal passages of adults passed to some extent through all types of face masks, even in the absence of coughing and sneezing. It should be pointed out, however, that they used a four-layer gauze mask in their study and not the more efficient mask with an inner layer of sheet cotton. Abramson<sup>30</sup> thinks that the use of the face mask in the control of droplet infection is an important integral part of preventive nursing and medical care, even though it is believed that such masks have an efficiency of only from 50 to 75 per cent. The criticisms of expense, difficulty in supplying and laundering and the tediousness of application are not valid arguments when reckoned in terms of protecting the lives of babies. Far from abandoning the face mask, efforts should be directed toward more efficient ones. The use of sheer-gauze masks

and of the paper masks should be eliminated in favor of those of more adequate construction, such as the absorbing or the deflector variety.

*Epidemic diarrhea of the newborn.* The recognition of epidemic diarrhea of the newborn is recent, most of the literature relating to it having appeared within the past decade. In general, the epidemics have had a significant mortality rate.

One of the problems in the control of epidemic diarrhea is the establishment of the diagnosis. Often the first cases develop so insidiously that the possibility of epidemic diarrhea is not considered and proper isolation is not provided until many other infants in the nursery have been exposed to the infection. Anderson and Nelson<sup>31</sup> recognize that there is often a tendency for loose and frequent stools, that overfeeding and improper artificial feeding may cause loose stools, that breast-fed babies frequently have stools postprandially, that drugs, laxatives and food irritants ingested by the lactating mother may cause loose stools in the infant and that parenteral infection or an enteritis due to dysentery organisms may be the cause of diarrhea. In order to protect other infants, however, they advise the isolation of an infant with diarrhea whenever any of the aforementioned conditions cannot be readily incriminated, as well as the provisional diagnosis of epidemic diarrhea of the newborn whenever two or more infants are similarly affected.

Tyson<sup>32</sup> finds it difficult to decide whether epidemic diarrhea is a disease entity in itself or part of a symptom complex. In three epidemics he observed, three different organisms were cultured from both the stools and the blood stream — *Streptococcus haemolyticus*, *Pseudomonas aeruginosa* (pyocyaneus bacillus) and *Escherichia coli* (colon bacillus).

Although a virus etiology for many of the epidemics of diarrhea in the newborn has been suspected it remained for Buddingh and Dodd<sup>33</sup> to demonstrate a virus in one epidemic. These authors had been studying a stomatitis of infants and children that was often accompanied by diarrhea and had demonstrated a hitherto unrecognized virus isolated from the mouths and stools by inoculation of the scarified rabbit cornea. In October, 1943, one of a pair of premature twins in a nursery was found to have stomatitis and diarrhea. Within the next few days several other infants developed the infection. In spite of immediate strict isolation precautions, 16 of the 30 infants in the nursery developed diarrhea within the course of the next two weeks. Although a mild stomatitis was present in 10 of the 16 infants, the outstanding feature of the diseases was diarrhea. Swabs obtained from the mouths and stools of all the affected infants produced characteristic lesions when inoculated upon the cornea of a rabbit. Swabs from the 14 unaffected babies produced no lesion.

Mouth swabs from 3 of the 4 nurses in charge of the nursery were also found to be positive for the virus. Two of the nurses at no time had lesions in



their mouths, but the third developed stomatitis during the week following the outbreak of diarrhea in the nursery. She carried the infection home to her own children, who were six and eight years old, and three months later her mouth swabs were still positive for the virus. Mouth swabs from 2 of 60 adults who were more or less directly engaged in caring for children in the nurseries and pediatric wards were positive for the virus without any accompanying symptoms. One of these carriers was an intern who had taken charge of the nursery after the epidemic of diarrhea had ceased. Four days later 3 new cases of stomatitis and diarrhea developed. Substitution of this intern for another, known to be free of virus, and isolation of the 3 infants controlled further spread of the disease.

When confronted with the possibility of an epidemic of diarrhea in the newborn, time is a factor and treatment cannot wait for the results of laboratory investigation. The plan of treatment at both the Boston Lying-in and Children's hospitals<sup>34</sup> calls for an immediate threefold system of isolation: physical isolation of infected patients; physical isolation of all contacts; and physical isolation of all new admissions from contact with either of the two preceding groups. Active treatment of infected patients is based on the suggestions of Twyman and Horton,<sup>35</sup> which are as follows: succinylsulfathiazole (sulfasuxidine) 1 gr. per pound of body weight per day; opiates by mouth; vitamin K, plasma or whole-blood transfusions; parenteral fluids; and protein milk formulas. In addition to the above procedures the infants are given from 12,000 to 24,000 units of penicillin per day in divided doses every three hours. The rationale of this treatment is that the sulfasuxidine combats enteric infection, if present, that the penicillin combats parenteral infection, if present, and that, if the disease proves to be of virus origin, nothing of a specific nature can be done beyond the general supportive measures outlined. The justification of this "shot-gun" approach is the high mortality associated with diarrheal disease.

In the epidemic of diarrhea of the newborn studied by Anderson and Nelson<sup>31</sup> a low carbon dioxide combining power of the blood was observed in 50 per cent of the cases in which abnormal clinical manifestations were noted, in spite of the fact that most of these infants did not exhibit the classic picture of acidosis. Significant clinical improvement attended the correction of the acidosis by the parenteral administration of a 5 per cent solution of sodium bicarbonate or of a 1M/6 solution of sodium lactate.

They emphasized the importance of constant observation of the ill infants and on the determination of the carbon dioxide level of the blood whenever there are evidences of increasing severity of the disease, with or without the usual manifestations of acidosis. 1101 Beacon Street

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31021

#### PRESENTATION OF CASE

A fourteen-year-old boy was admitted to the hospital because of abdominal pain and convulsions.

Three weeks prior to admission, while playing football, he was kicked in the right eye. Although he felt dizzy, he did not lose consciousness and was able to resume play. His eye subsequently became swollen and ecchymotic. During the following week he complained a good deal of abdominal discomfort and took soda for relief. About a week later, one week before entry, he was awakened from sleep by severe abdominal pain accompanied by nausea and vomiting. He was given an enema and on getting out of bed appeared confused and unable to find the door. While straining to expel the enema he suddenly became stiff, breathless, cyanotic and then limp and unconscious. He regained consciousness after five minutes. He was not incontinent and did not bite his tongue. There was no headache following the seizure, and he had no recollection of what had occurred. He was admitted to a community hospital where four similar attacks occurred during the next twenty-four hours. He vomited large amounts of dark-brown material. Although he failed to move his bowels for three days, an enema at the end of that time produced good results. The white-cell count was reported to be 19,000, and a roentgenogram of the abdomen was said to show dilated loops of small intestine. He was transferred to this hospital for study.

Physical examination revealed a pale, lethargic but oriented boy in no acute distress. There was slight ecchymosis around the right eye. The pupils, ocular movements, visual fields and fundi were normal. The heart and lungs were negative. The abdomen was tense, distended and tympanitic, with some tenderness and audible peristalsis in the lower abdomen. Neurologic examination was essentially normal.

The temperature was 99.2°F., the pulse 118, and the respirations 20. The blood pressure was 140 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 12.8 gm. per cent. The urine had a specific

\*On leave of absence.

gravity of 1.022, with a + test for albumin; the sediment contained an occasional red and white cell and a rare hyaline cast per high-power field. The blood serum nonprotein nitrogen was 23 mg. per 100 cc., and the protein 6.4 gm. per 100 cc., with an albumin-globulin ratio of 2.6; the serum chloride was 86 to 96 milliequiv. per liter. A blood Hinton test was negative.

Roentgenograms of the abdomen revealed several dilated loops of small bowel extending across the midabdomen. Considerable gas was seen in the colon but none in the rectum. A barium enema passed without delay from rectum to cecum and revealed no abnormality of the colon. The appendix was negative. The terminal ileum filled for a distance of 5 cm., at which point the barium column terminated rather abruptly; a post-evacuation film showed moderate contraction of the colon, but no further retrograde passage of barium in the terminal ileum. An x-ray examination of the skull was negative.

A Miller-Abbott tube was inserted into the duodenum with some difficulty and several hundred cubic centimeters of fluid was aspirated. After intubation, x-ray films failed to reveal the dilated loops of small bowel previously observed. The nausea and vomiting continued; the urine output was low, and fluids were administered parenterally. Except for the expulsion of the barium enema, the patient did not move his bowels after entry into the hospital. On the night of the fifth hospital day he awakened suddenly with a cry and complained of burning pain in the upper abdomen accompanied by a bearing-down sensation as if he wanted to move his bowels. The temperature rose to 102°F., and the abdomen was boardlike and acutely tender. An emergency laparotomy was performed that night.

#### DIFFERENTIAL DIAGNOSIS

DR. ARTHUR W. ALLEN: May we see the x-ray films before we start the discussion?

DR. MILFORD SCHULZ: This film, taken shortly after entry, shows the dilated loops of small bowel. There is a little gas in the colon here and there, but the colon is not dilated. On the film made after filling the colon with barium, you can still see the gas in the bowel; the small bowel is dilated but the terminal ileum is not. It is interesting that the appendix, which is filled, apparently is movable—at least the relation between the appendix and the cecum changed following evacuation. In the film taken three days later there is still a residue of barium in the bowel and most of the small bowel has been deflated.

DR. CHESTER M. JONES: Where is the Miller-Abbott tube? In the upper ileum?

DR. SCHULZ: I should say that it was either in the proximal ileum or in the distal jejunum.

DR. ALLEN: I wonder how he knows that.

DR. JONES: That is what I wonder.

DR. SCHULZ: It is not in the distal ileum because it is not near the cecum and there is quite a bit of tube present for it to be in the proximal jejunum.

DR. JONES: I agree.

DR. ALLEN: Having just listened to an excellent discussion of a patient who had two lesions,<sup>1</sup> one wonders whether, by any chance, luck will hold and whether this boy also had two conditions. It is difficult for me to connect his apparently minor injury to the orbit during a football game with the gastrointestinal story. When I first read the abstract I thought that this might well have been a serious injury to the head and that this boy might have had a Cushing syndrome of peptic ulcer on a central-nervous-system basis. As I read farther I thought that he might conceivably have had a peptic ulcer associated with a Meckel's diverticulum containing gastric mucosa. During the week following injury he had a sufficient amount of abdominal discomfort to take soda, and it says "for relief" not "with relief"; one wonders whether this boy did have something that caused gastric hyperacidity.

He got on extremely well, however, until about a week later, that is, two weeks after injury and one week before entry, when he was awakened from sleep by severe abdominal pain accompanied by nausea and vomiting. If he had an ulcer of the stomach that had actually perforated he certainly would have been awakened from sleep. He might have been nauseated and he might have vomited, but it does not appear that he was quite ill enough or that the onset was quite sudden enough for it to be a perforation of an ulcer.

The fact that he was confused following an enema and then had a so-called "convulsion,"—he is said to have become stiff, breathless, cyanotic and then unconscious,—is not particularly helpful because a considerable number of people faint after an enema. It is not unusual for persons to be confused in the middle of the night if they are sleepy, and they might even take the wrong turn and go through the wrong door under these circumstances. We had a man brought in here a few years ago who had just returned from his summer place, where the bathroom entrance was to the left; on arising at night, he, out of habit, turned in this direction instead of to the right, where his town-house bathroom was located, and stepped into an elevator well, falling four flights.

The patient we are discussing here was admitted to a community hospital and had four similar attacks. I suppose that means that he had four periods of unconsciousness. I do not know whether the phrase "similar attacks" means that he also had an enema and severe pain, but I assume that he did not have an enema each time he lost consciousness. He did vomit large amounts of dark-brown material. That may be significant since, if he had a perforated viscus, he would not vomit

large amounts of this material unless the perforation was low in the gastrointestinal tract. It is possible that this dark-brown material contained blood, because a patient who is vomiting a good deal will have a certain amount of bleeding from the mucous membranes. On the other hand one wonders if, by any chance, this was small-bowel content that was being vomited. The fact that the enema at the end of three days produced a good result from the colon is of no help except to say that the disease was not in the colon. It only means that he had an accumulation of fecal matter in the colon that had been there prior to the acute illness and that the enema removed some of this fecal material. During the period that he was in the community hospital the white-cell count was said to have been 19,000. We have no mention of white-cell counts after admission here, but I am sure that they were done and should like to know what they were.

DR. BENJAMIN CASTLEMAN: None are recorded.

DR. ALLEN: Of course they were done, but sometimes they do not get recorded. At any rate I shall assume that the count before entry was a comparatively correct figure. It is reasonable to suppose that a secondary inflammatory process was going on, some process that was damaging or at least impairing the blood supply to some segment of the bowel. I suspect that the increased white-cell count was not due to the "black eye."

The physical examination does not help us much, except that at the time he was examined he was not in acute distress, which means that he did not have a continuing process but something that came and went to some extent. That practically rules out the possibility of his having a perforation of a high viscus, unless one can conceive of a perforation that sealed itself off and reperforated; I doubt that this could recur so many times as is described here.

We shall have to accept the fact that neurologic examination was essentially normal. I do not know whether "essentially" is put in for a reason or whether it was entirely normal. There is one small fact—a systolic blood pressure of 140 is abnormally high for a boy of fourteen. He had a slight amount of albumin in the urine and an occasional hyaline cast, both of which might go with an illness of this severity; also there was abnormality in the albumin-globulin ratio, which could have been due to dehydration. The chloride was slightly low.

We know from the roentgen films of the abdomen that he had small-bowel obstruction of some sort. From the film after the barium enema I have to deduce that the obstruction was fairly low in the ileum; the barium certainly stops short at that point as if there were a string around the bowel, or a tumor or gallstone blocking it in that region. It might have been due to a tight band across the bowel. Certainly this is an extremely sharp demarcation in the barium column and therefore suggests a complete, total obstruction at that point.

The patient was observed for a period of five days and did well with Miller-Abbott decompression of the small intestine. We now have reached a point nine days after the acute onset of the abdominal difficulty and four weeks after the football injury, and it is difficult for me to visualize any injury to the abdomen that took place in the football game that would produce this picture. It is also difficult for me to associate the minor injury to the orbit with anything going on later, particularly with a negative neurologic examination and a negative skull plate. So I believe that this sudden episode that happened on the night of the fifth hospital day was something different, probably a complication of the intestinal obstruction. I assume that the sudden pain with a bearing-down sensation was due to a perforation in this region or at least to an extravasation of fluid into the pelvis, since this type of irritation is sometimes seen in acute episodes. Often when an acutely inflamed appendix is lying in the pelvis a patient has exactly this same bearing-down feeling, a desire to move the bowel, usually with no relief.

So in summing up this case I believe that this boy's football injury had nothing to do with his abdominal difficulty. He did have a contusion to his orbit, but he coincidentally began to get into gradual difficulty with his abdomen; this was something rather severe that ended in total small-bowel obstruction in the region of the terminal ileum. This picture probably could not be due to a Meckel's diverticulum. If this boy had an inflammatory process from a Meckel's diverticulum, there would almost surely be a tendency to fill some of the terminal ileum after evacuation of the barium enema. I do not know what could cause this sudden obstruction, but I think that there are two possible explanations. One is that he had a band of adhesions across this area that produced obstruction at this point. I should expect, however, if that had been the case, that he would not have got along so well as he did for the first four days of his illness, that is, before the Miller-Abbott intubation. The only other thing that I can think of to explain such a picture in a boy of this age—obviously it could not have been gallstone ileus, at least I do not believe that it could have been—is that he had an intussusception of the terminal ileum, which is most unusual. Ordinarily intussusception occurs from the ileum into the cecum, but small-bowel intussusception has been reported: Dr. Harvey Stone,<sup>2</sup> of Baltimore, has recently reported a case in which a polyp of the small intestine produced intussusception of the small bowel with obstruction. I believe that is a likely possibility in this case. I can go no farther, however; I believe that the football injury and the small-bowel obstruction were independent.

DR. LELAND S. MCKITTRICK: Dr. Schulz, would the abrupt cessation of the barium in any way sug-

gest that the obstruction was due to intussusception?

DR. SCHULZ: Ordinarily, the barium runs around the intussusceptum for a short distance or one can see the leading tumor in the barium. Usually it does not cut off so abruptly as this.

DR. ALLEN: This boy probably had an unusual amount of edema around the area, owing to the four days of obstruction prior to the barium enema.

DR. SCHULZ: Yes; I presume that it would take some effort to cause barium to run through such an area of intussusception.

DR. ALLEN: Do you often see an area as completely trapped as the one shown here?

DR. SCHULZ: It is possible. Will a diverticulum loop itself around the bowel?

DR. ALLEN: Yes. A diverticulum can do almost anything. Most of the patients with Meckel's diverticulum are operated on under the diagnosis of intestinal obstruction.

DR. CASTLEMAN: But the obstruction is higher up.

DR. ALLEN: Yes, but usually close to the ileocecal valve. I do not believe that it was a diverticulum.

DR. CASTLEMAN: Dr. McKittrick operated on this boy. Will you tell us about your findings?

DR. MCKITTRICK: As Dr. Allen has said, this case was puzzling. We followed through essentially the same line of reasoning, but since we were not up before a clinicopathological conference, we did not have quite the same urge to explain the cause of an obstruction that was obvious when one saw the x-ray films. We had a little trouble with the Miller-Abbott tube, but it did pass the pylorus and did a good job of deflating him. On the afternoon before operation, the abdomen was quite soft and non-tender, and I thought that he was doing extremely well. I was called at about four o'clock the next morning because the patient had been awakened by sudden pain. I came down and operated on him with a working diagnosis of acute small-bowel obstruction with perforation. We had not committed ourselves to the cause of the obstruction.

There was a slight delay in getting under way, through no fault of anyone in particular, but it was approximately two hours after the perforation when the abdomen was opened. The peritoneal cavity did not contain so much fecal material and intestinal contents as I had anticipated. There was widespread purulent material and obvious generalized peritonitis. A distended edematous small bowel presented itself, and by putting the hand into the abdomen I could feel the point of obstruction. As gently as I could I lifted it out and saw two open ends, the small bowel being completely divided. How much of that I had done and how much had been done in the small hours of the morning I do not know. It is quite possible that the balloon of the Miller-Abbott tube saved this boy's life by preventing the escape of the small-bowel contents into the abdominal cavity. It not only had deflated the obstructed segment but the tube, being still inflated

and located 5 cm. above the perforation, had acted as a cork to prevent complete emptying of the bowel into the peritoneal cavity.

We, too, were intrigued by the abrupt cessation in the passage of barium. We did not know what it meant. At operation the obstruction was well above the ileocecal valve and had nothing to do with the x-ray finding.

DR. ALLEN: That was the red herring.

DR. McKITTRICK: There were lymph nodes up to 1.5 cm. in diameter and a great deal of edema. I thought that the boy had a tumor of the small bowel that had ulcerated through. We resected the segment of ileum and did an end-to-end anastomosis, closing the abdomen without drainage. He was given sulfadiazine intravenously. A pelvic mass developed but cleared up without operation. The wound remained clean, and he had an uneventful convalescence. I should like to re-emphasize the fact that the Miller-Abbott tube with the distended balloon going to the point of obstruction and occluding the outflow of material from above probably saved this boy's life.

#### CLINICAL DIAGNOSIS

Acute small-bowel obstruction, with perforation.

#### DR. ALLEN'S DIAGNOSIS

Subacute small-bowel obstruction, with gangrene and perforation, probably from intussusception.

#### ANATOMICAL DIAGNOSIS

Ileocecal intussusception, with gangrene and perforation.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The specimen we received showed a large porky mesentery, as Dr. McKittrick mentioned, which was composed of inflammatory edematous fat. The tumor-like mass in the ileum proved to be an intussusception of 7 cm. of the ileum, which had become gangrenous. That is why it broke in half. I believe that the boy had it at the time of the first attack of abdominal pain, three weeks before he was operated on, and that that accounted for the extreme necrosis of the bowel, which was black.

DR. McKITTRICK: I just asked Dr. Allen if he had ever seen an intussusception of the ileum without something to lead it.

DR. CASTLEMAN: We sectioned the entire specimen and could find no evidence of tumor. It is possible that there had been a polyp, but the bowel had become so gangrenous that we could not recognize it.

DR. ALLEN: It might have sloughed off.

DR. CASTLEMAN: That is possible, but there were no polyps elsewhere in the specimen.

DR. ALLEN: I would like to take issue with you on the statement that this intussusception had

existed for four weeks. It is possible to get dead gut in a matter of four days. Is it not possible that this boy had intermittent intussusception during the first three weeks of his sickness, which was at least two weeks before he finally became completely obstructed? His complete obstruction, I believe, dates from the night he was awakened with the severe abdominal pain.

DR. CASTLEMAN: I think that is true. I did not mean that he had complete obstruction for four weeks but that he had intermittent intussusception during this period, with frequent injuries to the ileum in the region of the intussusception.

DR. JONES: Can you recall how many cases you have had with true ileal intussusception without a tumor?

DR. CASTLEMAN: It must be extremely rare. I do not recall another case, but as Dr. Allen mentioned, the tumor may well have sloughed off.

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#### CASE 31022

#### PRESENTATION OF CASE

A forty-three-year-old woman was admitted to the hospital with dysphagia and headache.

The patient was in apparent good health until two and a half months prior to admission, when she noted difficulty in swallowing liquids. Attempts to drink milk, for example, were followed by choking and she had difficulty in getting her breath. The dysphagia was not always present, and she apparently had no difficulty in swallowing solid foods. She also noticed that her voice was weak and hoarse. Lying down at night brought on a feeling of oppression in the chest, which was not relieved by sitting up. A sense of obstruction was present in the throat, resulting in constant unproductive attempts to clear the throat. There was no cough or expectoration. Three weeks before entry she developed a severe pounding headache aggravated by motion. It was worse in the morning, often beginning as a generalized throbbing and finally localizing in the right temple. Two weeks prior to admission she noted marked weakness of the right arm and was unable to control its movement when reaching for things. The legs felt stiff, and she seemed unable to lift them. Sharp pains were present in the left leg. About four months before admission the patient had several episodes of pain and fullness in the epigastrium that came on about an hour after meals. The distress was relieved to some extent by a hot-water bottle but not by food. A local physician made a diagnosis of gastric ulcer by fluoroscopy. Following treatment the symptoms

disappeared, and at the time of admission she had been free of epigastric distress for three months.

Physical examination revealed a poorly developed, emaciated and dehydrated woman with a weak, hoarse voice. The breasts were poorly developed but otherwise negative. There was no adenopathy. The pupils reacted to light and accommodation. The gait was shuffling. The Romberg sign was positive. The right shoulder drooped and could not be raised; the muscles of the right shoulder and upper arm showed hypotonicity and some atrophy. There was a tendency toward "winging" of the right scapula. All the deep tendon reflexes were hyperactive, more so on the right. The right lower abdominal reflex was diminished. The plantar responses were flexor in type bilaterally. The finger-to-nose and heel-to-knee tests showed awkwardness and overshooting bilaterally, but more so on the right.

The temperature was 98.6°F., the pulse 94, and the respirations 20. The blood pressure was 116 systolic, 70 diastolic.

Examination of the blood showed a red-cell count of 4,520,000, with 14 gm. of hemoglobin, and a white-cell count of 8500, with 60 per cent neutrophils. The urine and stools were negative. The serum protein was 6 gm. per 100 cc.; the blood sugar and the serum nonprotein nitrogen were normal. A tuberculin test in a dilution of 1:1000 was negative. A Hinton test was negative.

A roentgenogram of the chest revealed a few linear shadows in the left third and fourth interspaces anteriorly. An ill-defined shadow was present in the region of the left hilus. An x-ray examination of the skull was negative. Two electroencephalograms taken soon after admission revealed a diffuse spotty dysrhythmia without consistent focal distribution but generally worse toward the occiput.

A lumbar puncture revealed clear colorless fluid. The pressure was normal initially and responded normally after jugular compression. No cells were present; the protein content was normal, and the Wassermann test was negative. An examination of the larynx revealed complete paralysis of the left vocal cord, which lay in the so-called "cadaveric position." The right cord functioned normally.

On the twentieth hospital day the temperature gradually began to rise, reaching 102°F. over a period of about thirty-six hours. She developed some cough, raising a small amount of sputum, and there was pain over the left anterior chest on coughing. The left apex and upper chest were dull to percussion, with bronchial breath sounds anteriorly and an expiratory grunt. There were coarse rales over the left apex posteriorly. The liver was palpable two fingerbreadths below the costal margin. A sputum culture revealed alpha-hemolytic and a few beta-hemolytic streptococci, and a blood culture was negative. The white-cell count was 24,000. A catheterized urine specimen was negative. A roentgenogram of the chest revealed irregular patchy

consolidation of the left upper lobe and a small amount of fluid in the posterior costophrenic sinus.

The temperature continued to range between 100 and 102.6°F. Respirations were shallow and rapid, and the patient appeared dehydrated and slightly cyanotic. She was treated with sulfadiazine and oxygen. On the twenty-sixth hospital day, the patient became jaundiced and a moderate amount of bile appeared in the urine. Sulfadiazine was stopped and penicillin substituted. She was also given potassium iodide because of difficulty in bringing up the tenacious sputum. Diffuse coarse rales were audible throughout the lung field.

On the thirtieth hospital day the patient began to improve. The temperature gradually fell to normal, and the sputum diminished in quantity. The icterus cleared completely, and the liver was no longer palpable. The lungs showed slight dullness over the entire left chest, with scattered fine and coarse rales, and normal breath sounds diminished over the left apex anteriorly. There was slight sacral edema. The total plasma protein was 5.3 gm. per 100 cc., with an albumin-globulin ratio of 0.93. The serum chloride was 90 milliequiv. per liter. A cephalin flocculation test was negative in twenty-four and  $\pm$  in forty-eight hours. X-ray examination of the chest revealed little change in the appearance of the left upper lobe.

The temperature continued to range between normal and 100°F., occasionally reaching 101°F. The neurologic signs originally noted became more marked, with extreme weakness of the right arm. A positive Hoffmann sign appeared on the right, but the Babinski signs were negative. Dullness and bronchial breath sounds reappeared over the left upper lobe and were accompanied by scattered fine rales and a cough, which was moderately productive of purulent sputum. Another chest film revealed no change in the left upper lobe, but the right lung field showed increased linear markings. Pleural fluid was present bilaterally. Several convulsions of the Jacksonian type occurred, each lasting several minutes. The convulsive movements started in the right hand and arm, spreading to the leg and face. The seizures were followed by drowsiness and sleep. On the fortieth hospital day a Babinski sign was elicited on the right and there was prolonged ankle clonus on the right. There was dullness to pinprick in the right leg. On the same day the patient had a convulsion followed by temporary aphasia.

She continued to cough and raise large quantities of green mucoid sputum. She became unco-operative, refusing all food and medication. The chest signs continued unchanged. She became extremely weak and drowsy and expired on the fifty-third hospital day following a convulsive episode.

#### DIFFERENTIAL DIAGNOSIS

DR. ARTHUR LINENTHAL: The problem in this patient appears to be one of disease involving structures within the chest as well as the central nervous

system. Consideration of the neurologic lesion may appropriately follow discussion of the chest difficulty, since I think that the two are interrelated.

The presenting symptoms of this patient were difficulty in swallowing, difficulty in breathing, a sense of oppression in the chest, a sense of obstruction in the throat, and weakness and hoarseness of the voice. The complete paralysis of the left vocal cord, fixed in the cadaveric position midway between phonation and quiet inspiration, and the ill-defined x-ray shadow in the left hilar region suggest that these findings as well as the symptoms may have been due to some process in the left hilar region involving the left recurrent laryngeal nerve and pressing on the esophagus and trachea. The emaciated condition of the patient on admission is consistent with the impression that a malignant neoplasm was the likeliest basis of such a process.

Regarding the primary site of such a tumor, bronchiogenic carcinoma seems most probable, although other locations must be considered. It is interesting that there had been no cough and no sputum before the patient entered the hospital, but this does not rule out a pulmonary neoplasm.

The statement that a gastric ulcer had been seen by fluoroscopy raises the question whether there was a gastric neoplasm with metastases to the hilar nodes and surrounding structures. Since the abdominal symptoms that led to the fluoroscopy subsided, x-ray studies of the stomach were not repeated, and we have no evidence on which to settle this question.

There is no evidence for other diseases that might have given rise to the presenting symptoms and physical findings. Neither physical examination nor x-ray examination showed evidence of an aortic aneurysm, and examination of the larynx did not reveal any intrinsic disease. Esophageal carcinoma might well have explained the presenting picture, but since no studies of the esophagus were made, there is no way to confirm this diagnosis.

At the end of the third week in the hospital, the patient developed a pulmonary infection in the left upper lobe. This was marked by fever, cough, sputum and pain over the left chest. The respirations were rapid and shallow, and she became cyanotic. Physical examination gave evidence of consolidation over the left upper lobe, and this was confirmed by x-ray. Elevation of the white-cell count suggests a bacterial etiology, but the sputum showed only alpha-hemolytic and a few beta-hemolytic streptococci. She was given sulfadiazine and then penicillin, but there is no evidence that these were of value. The patient improved, the physical findings over the left upper lobe diminished but never entirely disappeared, and the x-ray picture showed little change.

It is interesting that this severe pulmonary infection developed in the left upper lobe, since the

lesion that I have supposed to exist at the left hilus could easily have compressed the left upper lobe bronchus and caused some increased susceptibility to infection in that area. The linear shadows seen in the third and fourth left interspaces on the first chest film may have represented small areas of atelectasis.

At the time of the development of the pulmonary infection, before the patient had received any chemotherapy, the liver was found to be enlarged. Subsequently she was given sulfadiazine, and while receiving the drug, she became jaundiced and had bile in the urine. The sulfadiazine was stopped and soon afterward, along with improvement in the pulmonary condition, the jaundice disappeared and the liver became smaller.

It is difficult to be sure of the relation between the pulmonary infection, the sulfonamide therapy and what appears to have been an episode of acute hepatitis. Toxic hepatitis has been described after sulfadiazine, but the presence of the hepatic enlargement in this case before sulfadiazine was given makes me believe that the sulfa drug was probably not responsible. Bacterial pneumonia may be accompanied by jaundice. There is also the possibility that both the pulmonary infection and the hepatitis were due to a virus infection. The negative cephalin flocculation test done at about the time the jaundice was subsiding suggests that the degree of liver damage was slight. No other liver function tests were done. The plasma proteins showed no significant change.

Obstructing lesions of the biliary tract must be mentioned, but there is nothing to support such a diagnosis and the transient hepatic enlargement is suggestive of intrahepatic disease. There was apparently no abdominal pain at that time, and there is no evidence for gallstones. Metastatic disease of the liver or around the bile passages seems too remote to be seriously considered.

The pulmonary infection never entirely cleared up, and indeed at the time of death there was an increase in the physical findings, as well as a persistence of the x-ray abnormalities over the left upper lobe and the development of purulent sputum. Apparently the infection was a persistent one, either because of some blockage of drainage from the involved lobe or because of the characteristics of the infectious process. This may well have been a virus disease with superimposed bacterial infection.

The acuteness of the onset of the pulmonary infection, together with the absence of clinical or x-ray evidence of pulmonary tuberculosis on admission, seems to eliminate tuberculosis as a possibility. Unfortunately there is no record of a search for tubercle bacilli in the sputum.

The neurologic disorder was, I think, related to the disease in the chest; that is, it was caused by a metastasis of the malignant process. The problem

here is to decide on the basis of the evidence presented how many neurologic lesions were present and where they were located.

The terminal neurologic findings were marked. The weakness in the arm, the appearance of a Hoffmann sign, the development of Jacksonian convulsions starting in the right arm and hand, the appearance of a Babinski sign on the right with ankle clonus, the increase in the deep tendon reflexes on the right and the episode of temporary aphasia point to a lesion in the left cerebral hemisphere involving primarily the motor area for the arm with extension to the motor area for the leg and to the nearby speech area. Sensory changes, such as the late dullness to pinprick in the right leg, suggest subcortical extension of the process.

The earliest manifestation of any neurologic disorder was the development of weakness in the right arm. Subsequently the muscles of the right arm and the right shoulder girdle showed atrophy. This finding suggests a metastatic lesion involving the anterior-horn cells of the right side of the mid-cervical spinal cord. There was hypotonicity, but the deep tendon reflexes were also increased. The atrophy can be explained on the basis of weakness of the right arm with resulting disuse. The stiffness in both legs at the onset is difficult to explain. The positive Romberg sign and the evidence of incoordination on admission may be attributed to weakness. It seems, therefore, that all the findings can be explained on the basis of one metastatic cerebral lesion.

The patient went down hill rapidly and died following a convulsive seizure, probably owing to involvement of a vital nervous center.

#### CLINICAL DIAGNOSES

Tumor involving left motor cortex of brain  
(? primary, ? metastatic from bronchiogenic carcinoma).

Unresolved pneumonia: left upper lobe.

#### DR. LINENTHAL'S DIAGNOSES

Bronchiogenic carcinoma of left lung, with metastases to regional nodes and left cortical and subcortical regions of brain.

Unresolved pneumonia: left upper lobe.

Acute hepatitis, subsiding.

#### ANATOMICAL DIAGNOSES

Carcinoma, oat-cell type, of left upper lobe, with metastases to bronchial, mediastinal, mesenteric and retroperitoneal lymph nodes, liver, kidney and brain.

Chronic pneumonitis: left upper lobe.

Bronchiectasis: left lower lobe.

Cerebral pressure cones.

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: As Dr. Linenthal predicted, the pulmonary and cerebral lesions were related. This woman did have a bronchiogenic carcinoma, the primary focus being in the bronchus to the left upper lobe, which was completely occluded. The metastatic bronchial and mediastinal lymph nodes had infiltrated the wall of the left main bronchus, especially the lower lobe bronchus. The latter was so narrowed that secondary bronchiectasis had developed throughout the lower lobe, the bronchioles being dilated and filled with purulent material. The primary tumor in the left upper lobe had extended into the parenchyma around the bronchus for about 4 cm., and the remaining pulmonary tissue in this lobe was gray and rubbery, characteristic of the so-called "drowned out" or "stasis" pneumonitis.

There were three cerebral metastases. The largest, and the one that caused most of the cerebral symptoms, was a cystic lesion measuring 6 by 3 by 2.5 cm. in the left parietal region. The other two, each about 2 cm. in diameter, were solid nodules, one in the right posterior frontal region and one in the posteroinferior portion of the right cerebellar hemisphere. There was definite evidence of increased intracranial pressure, as shown by flattening of the convolutions and the deep cerebellar and temporal pressure cones.

The liver weighed over 2000 gm. and contained many metastatic nodules. I do not believe, however, that there was sufficient replacement of parenchyma to have produced even the transient jaundice. A likelier explanation is the presence of many metastatic lymph nodes surrounding and compressing the common bile duct.

Microscopically the carcinoma was extremely undifferentiated, showing no tendency to either keratinization or gland formation. In many places it suggested the oat-cell type.



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## NOT SO GOOD

Two federal agencies that seem to have had some difficulty in retaining the confidence of the public, and between which close harmony is essential although its existence is not always apparent, are the War Food Administration and the Office of Price Administration. A duty of the WFA, through its carefully organized system of food experts, is to know month by month, as well as year by year, the food resources of the country and their proper allocation to the armed services, to lend-lease and to the civilian population. A function of the OPA is to effect and maintain a system of food rationing that will provide an equitable distribution of the country's resources so far as native intelligence and human honesty can assure it.

An example of the failure of these two agencies to co-ordinate their activities was furnished last fall when the WFA made public announcement that twelve pounds of butter per capita per year was available to the entire civil population. At that time butter was worth twenty red points per pound on the rationing list, and since each individual had available thirty points for each four-week period, no slide-rule expert was needed to apprise the concerned housewife of the fact that in order to obtain her promised butter she must give up two thirds of the points that also had to cover her expenditures for meat, cheese and other fats. As of Christmas night, moreover, the Magi whose guiding star shines over the Potomac presented a somewhat suspicious public with an increase in the point value of butter to twenty-four, and canceled many outstanding points that the thriftier housewives had been saving against a rainy day.

Thus are prudence and patriotism rewarded, and thus is the bewildered citizen encouraged to disregard the rules, since they have been changed in the middle of the game. As the *Boston Herald* notes in the leading editorial of December 27, 1944: "A government that repudiates its currency forfeits the confidence of its people. We can ill afford to lose faith in the Office of Price Administration, but its action in canceling certain unspent red, blue and sugar stamps is unpleasantly akin to currency repudiation."

It is not implied that butter is an essential kind of food; we can do without butter, as many of us have already learned. What we cannot dispense with is confidence in the agencies that are attempting to lead us through our wilderness. Probably the worst that can be said is that, like some of our military leaders, they simply did not know what was going on. In that lack of knowledge, however, they have lost face with the public to which they are eventually answerable. This has made it more difficult, moreover, for some of the volunteer citizen aides, such as the members of medical advisory committees, to solve their own problems conscientiously and to retain to any great degree the confidence of their own "public."

This country can double and triple and quadruple the sacrifices that it is making, and may yet have

to do so now that its introductory years to total war are over. It can do so with calm confidence, however, only if it can have faith in the judgment and ability of its leaders, as well as in their integrity: and this last is not being questioned. If democracy at war may be considered as passing through a forest of disillusionment guided only by a flickering lamp of patriotism, then let us at least turn our ingenuity to trimming the lamp and not to extinguishing it.

## EARLY DIAGNOSIS OF TYPHUS FEVER

THE medical profession and the lay public of New England are not particularly concerned with typhus fever. This disease is a clinical curiosity in most parts of this country, particularly in New England. In many other parts of the world, however, it is of frequent occurrence and is always a serious problem. Members of our armed forces are now to be found in almost all the countries in which this or similar rickettsial diseases are both endemic and epidemic. The present war has stimulated considerable interest and activity in this field, and great strides forward have been taken in the recognition and prevention of many of the rickettsial diseases. Among the Russian investigators who have made notable contributions is Professor A. A. Smorodintsev, chief of the Virus Disease Division of the All Union Institute of Experimental Medicine in Moscow, who visited this country last year.

One of the most significant aspects of any program of prevention or eradication of an infectious disease is its early recognition. The diagnosis of typhus fever in the past has depended on the Weil-Felix reaction. This is a test for agglutinins against certain strains of the proteus bacillus in the serum of the patient. It depends on the empirical observation that such antibodies appear during the latter part of the illness, and during convalescence, of certain rickettsial diseases, including typhus fever. It is, therefore, not a highly specific reaction. Furthermore, positive results are not obtained until after the fifth day and usually only after the first week.

Smorodintsev and Drobyshvskaya<sup>1</sup> have recently described a complement-fixation test that is designed to detect the presence of antigen in the

serum of patients during the earliest stages of the disease. This test, therefore, has the advantage of giving the earliest possible diagnosis and probably is also more specific. It involves the use of suitably chosen convalescent serums from recovered patients, but serums from hyperimmune rabbits will presumably prove equally satisfactory or even better. The test is carried out by mixing immune serum with inactivated serum from the patient in the presence of suitable amounts of complement, and then testing for the fixation of complement with a suitable hemolytic system.

With this test, a positive diagnosis was made in all patients from whom serum was obtained during the first two days of the disease and in about 60 per cent of those from whom the serum was obtained between the third and sixth days of the disease. Positive Weil-Felix reactions did not occur in any of the serums obtained during the first four days of the disease, and this test was positive in only 38 per cent of the serums obtained on the fifth and sixth days. Moreover, between the fifth and eighth days of the disease, positive tests were obtained in one third of the serums only by the complement-fixation test and in another third only with the Weil-Felix reaction, the remaining serums being either positive or negative to both tests.

It is thus seen that in the first days of the disease this complement-fixation test is almost completely reliable, while during the latter part of the first week of the disease and possibly during the early part of the second week, the use of both the complement-fixation and Weil-Felix tests should give a positive diagnosis in at least two thirds of the cases. Although the principle involved in this method — namely, the detection of a circulating antigen early in the course of the disease — is not new, it has never before been applied in exactly this manner. It has been used to detect the type-specific soluble substance of the pneumococcus in the blood of patients early in pneumonia.<sup>2</sup> It has also been used to detect precipitinogen in early cases of yellow fever.<sup>3</sup>

Recent attempts to devise a diagnostic method more useful than the Weil-Felix reaction have resulted in a technic employing a rickettsial antigen prepared from agar tissue cultures in

a complement-fixation test,<sup>4</sup> but it is obvious that such a procedure measures *antibody* rather than *antigen* in the patient's serum and that it is less likely to give a positive reaction early in the course of disease than is a test for antigen.

Since much of the work on typhus fever that has been done by workers in this country and in Great Britain is confidential and has not been published, it is more than likely that extensive observations have already been made with respect to the application of this test and possibly of others that are equally useful. The results of these and other observations will determine whether the test suggested by the Russian workers is a valuable clinical aid, and further study may reveal other virus or rickettsial diseases to which this principle may be adaptable for early diagnosis.

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## MISCELLANY

### HOSPITALS APPROVED FOR GRADUATE TRAINING IN SURGERY

The American College of Surgeons has recently announced that two hundred and thirty-one hospitals in the United States and Canada have been approved for graduate training in general surgery and the surgical specialties. In announcing the list, Dr. Malcolm T. MacEachern, associate director, states that surveys of five hundred or more hospitals offering opportunities for graduate training in surgery are planned during the coming year, the increased emphasis on this work being stimulated by the need for providing ample opportunities for resumption of training by medical officers when they return from service with the armed forces. The College helps hospitals to organize graduate training programs to meet the requirements for approval, and also plans to aid physicians returning from service in resuming their training in surgery. The list of hospitals in Massachusetts is as follows:

HOSPITAL	APPROVED TYPE OF TRAINING
<i>Boston</i>	
Beth Israel Hospital (215 beds)	General surgery Urology
Boston City Hospital (2378 beds)	General surgery Neurological surgery Orthopedic surgery Urology
Boston Lying-in Hospital (138 beds)	Obstetrics
Carney Hospital (234 beds)	General surgery Obstetrics and gynecology
Children's Hospital (256 beds)	General surgery Neurological surgery Orthopedic surgery Otolaryngology
Lahey Clinic (New England Baptist Hospital—228 beds) (New England Deaconess Hospital—310 beds)	General surgery Neurological surgery Orthopedic surgery Urology Otolaryngology
Massachusetts Eye and Ear Infirmary (227 beds)	Ophthalmology Otolaryngology
Massachusetts General Hospital (851 beds)	General surgery Neurological surgery Orthopedic surgery Urology
Massachusetts Memorial Hospitals (414 beds)	General surgery Obstetrics
Peter Bent Brigham Hospital (108 beds)	General surgery Urology
<i>Brookline</i>	
Free Hospital for Women (101 beds)	Gynecology
<i>Worcester</i>	
Memorial Hospital (185 beds)	Otolaryngology

## CORRESPONDENCE

### SIGNED EDITORIALS

*To the Editor:* Having read the original editorial "Pharmacology and Anesthesia" with at least marked disagreement to many of the statements in it and certainly with curiosity as to who propounded them I am prompted again to suggest the wisdom of having editorials signed.

I know that this matter has already been once disposed of in opposition and with disapproval of this procedure, but I wish again to call attention to the fact that it would have so placed the responsibility for statements which are so contrary to the opinions of experienced anesthetists that I am certain that the author would have either hesitated to make them or have prepared himself more fully to support them.

It is still my conviction that the signed editorial bears greater weight and causes less confusion and even less harm than the unsigned one, which permits statements that would frequently not be made were it necessary for the author to sign his name to it.

FRANK H. LAHEY

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## BOOK REVIEWS

*Homicide Investigation: Practical information for coroners, police officers and other investigators.* By LeMoyne Snyder, M.D. With chapters by Captain Harold Mulbar, Charles M. Wilson and C. W. Muehlberger. 8°, cloth, 287 pp., with 116 illustrations. Springfield, Illinois: Charles C Thomas, 1944. \$5.00.

The purpose of this book in the words of its author is "to make available to coroners, police officers or others, whose duty it is to inquire into the nature of a homicide, tested practical plans of procedure to follow in adequately investigating the death." He refers to it as a synopsis of factual information intended to be of practical use to men without scientific training whose duties call them to investigate potentially violent deaths.

The book is well illustrated and written in simple language. It is particularly valuable in that it teaches what not to do as well as what to do. It covers the needs of the coroner or medical examiner who is isolated from larger centers, and also the progressive police chief. It includes a consideration of the value of methods of lie detection, based on the use of the Keeler polygraph, which is looked on as a valuable aid to crime detection. The work can be highly recommended as a practical guide for those for whom it is intended.

*Practical Malaria Control: A handbook for field workers.* By Carl E. M. Gunther, M.D., B.S., D.T.M. (Sydney). With a foreword by Prof. Harvey Sutton, O.B.E., M.D., F.R.A.C.P., B.Sc., D.P.H., F.R.San.I. 12°, cloth, 91 pp. New York: Philosophical Library, 1944. \$2.50.

The foreword by Prof. Harvey Sutton states that the author of this book, Dr. Carl E. M. Gunther, spent many years at Bulolo in the Mandated Territory of New Guinea as a field medical officer of a gold-dredging company. The seat of operations was in the midst of tropical forests where malignant tertian malaria was highly endemic. Dr. Gunther is an entomologist of repute, and a student of clinical and preventive medicine who is well acquainted with its literature; at present he is with the Australian Medical Corps.

The author offers the booklet in the hope that it may help those who are meeting malaria in the field with only an academic knowledge of the disease. Although adapted to local conditions in New Guinea, the author believes that his methods of dealing with malaria are applicable in other undeveloped districts where the population is widely scattered. The opinions expressed are based on experience gained during a period of ten years. The author recognizes that some of his views are radical, unscientific or dogmatically expressed. Dogmatism is justifiable, however, in so condensed an outline of the broad subject of malaria.

The reviewer finds that some of the author's statements regarding the absorption of quinine are of doubtful validity and that the author is in error when he says that quinine is directly toxic to all types of malaria parasites at all stages (evidently, Dr. Gunther forgot to take the sporozoite into consideration). The paucity of exact knowledge regarding the absorption and the action of quinine and other drugs in malaria, however, justifies differences of opinion.

The text contains many interesting observations. Practical methods of treatment are described in detail. The booklet should be of interest to students and of great value to medical field workers.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Practical Malaria Control: A handbook for field workers.* By Carl E. M. Gunther, M.D., B.S., D.T.M. (Sydney), field medical officer, Bulolo Gold Dredging Limited, Territory of New Guinea. With a foreword by Prof. Harvey Sutton O.B.E., M.D., F.R.A.C.P., B.Sc., D.P.H., F.R. San. I. 12°, cloth, 91 pp. New York: Philosophical Library, 1944. \$2.50.

*Radiation and Climatic Therapy of Chronic Pulmonary Diseases: With special reference to natural and artificial heliotherapy, x-ray therapy and climatic therapy of chronic pulmonary diseases and all forms of tuberculosis.* Edited by Edgar Mayer, M.D., assistant professor of clinical medicine, Cornell University Medical College, New York City, attending physician,

New York and Memorial hospitals, special pulmonary-consultant, New York State Department of Labor, and director (*ex urbe*) Northwoods and Will Rogers Tuberculosis sanatoriums, Saranac Lake, New York. 8°, cloth, 393 pp., with 46 illustrations. Baltimore: Williams & Wilkins Company, 1944. \$5.00.

This composite work of twenty-two authors reflects the present-day knowledge of the special treatment of chronic pulmonary diseases, including all forms of tuberculosis. Incorporated in the work are the clinical experiences of the editor and of many of the collaborators.

*Technique in Trauma: Planned timing in the treatment of wounds, including burns.* By Fraser B. Gurd, M.D., C.M., and F. Douglas Ackman, M.D., C.M., in collaboration with John W. Gerrie, M.D., C.M., Edward S. Mills, M.D., C.M., Joseph E. Pritchard, M.D., and Frederick Smith, M.D. with a preface by John S. Lockwood, M.D., University of Pennsylvania, and a commentary by Ralph R. Fitzgerald, M.D., C.M. McGill University. 4°, cloth, 68 pp., with 5 plates, 17 figures, 5 tables and 3 charts. Philadelphia: J. B. Lippincott Company, 1944. \$2.00.

This small monograph is composed of three articles that appeared in the *Annals of Surgery* in 1942, 1943 and 1944, with some additions to the text. The basis of the monograph is carried on at the Montreal General Hospital. The authors emphasize not only the importance of adherence to the basic physiologic principles, but also bring out the fact that these principles can only be applied to a large hospital by the use of sound planning and thorough teamwork.

*Industrial Ophthalmology.* By Hedwig S. Kuhn, M.D. 8°, cloth, 294 pp., with 114 illustrations, including 2 color plates. St. Louis: C. V. Mosby Company, 1944. \$6.50.

In this book the author attempts to co-ordinate much of the essential information relating to the various ophthalmologic problems that confront industry.

*Minor Surgery.* Edited by Humphry Rolleston and Alan Moncrieff. 8°, cloth, 174 pp., with 30 illustrations. New York: Philosophical Library, 1944. \$5.00.

This new manual in minor surgery is made up of eighteen articles on selected subjects, written by English authorities in their special fields. Although there is not any preface or foreword, it seems evident that this small work is published at this time for war reasons. The editing is well done and the various articles are short, emphasizing diagnosis and emergency treatment. The subjects covered include minor wounds, sprains, the foot and hand, the mouth, nose, throat and eye, bursas and ganglia, certain benign tumors and cysts, skin infections, the rectum, the genitourinary system, nonoperative treatment of hernias and the fitting of trusses and belts, varicose veins, ulcers and phlebitis, gynecology, the surgery of children, and anesthesia in minor surgery.

*Virus Diseases in Man, Animal and Plant: A survey and reports covering the major research work done during the last decade.* By Gustav Seiffert. 8°, cloth, 352 pp. New York: Philosophical Library, 1944. \$5.00.

In this small volume the author attempts to give a survey of the present status of virus investigations with special consideration of the most recent literature, especially that from foreign countries. The work discusses the important virus diseases of man, animal and plant, and its aim is to furnish an introduction to the study of the viruses.

*Homicide Investigation: Practical information for coroners, police officers and other investigators.* By LeMoyné Snyder, M.D., medicolegal director, Michigan State Police. With chapters by Captain Harold Mulbar, chief of the Identification Bureau, Michigan State Police, Charles M. Wilson, director, Chicago Police Scientific Crime Detection Laboratory, and C. W. Muehlberger, director, Michigan Crime Detection Laboratory. 8°, cloth, 287 pp., with 116 illustrations. Springfield, Illinois: Charles C Thomas, 1944. \$5.00.

a complement-fixation test,<sup>4</sup> but it is obvious that such a procedure measures *antibody* rather than *antigen* in the patient's serum and that it is less likely to give a positive reaction early in the course of disease than is a test for antigen.

Since much of the work on typhus fever that has been done by workers in this country and in Great Britain is confidential and has not been published, it is more than likely that extensive observations have already been made with respect to the application of this test and possibly of others that are equally useful. The results of these and other observations will determine whether the test suggested by the Russian workers is a valuable clinical aid, and further study may reveal other virus or rickettsial diseases to which this principle may be adaptable for early diagnosis.

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#### MISCELLANY

##### HOSPITALS APPROVED FOR GRADUATE TRAINING IN SURGERY

The American College of Surgeons has recently announced that two hundred and thirty-one hospitals in the United States and Canada have been approved for graduate training in general surgery and the surgical specialties. In announcing the list, Dr. Malcolm T. MacEachern, associate director, states that surveys of five hundred or more hospitals offering opportunities for graduate training in surgery are planned during the coming year, the increased emphasis on this work being stimulated by the need for providing ample opportunities for resumption of training by medical officers when they return from service with the armed forces. The College helps hospitals to organize graduate training programs to meet the requirements for approval, and also plans to aid physicians returning from service in resuming their training in surgery. The list of hospitals in Massachusetts is as follows:

HOSPITAL	APPROVED TYPE OF TRAINING
<i>Boston</i>	
Beth Israel Hospital (215 beds)	General surgery Urology
Boston City Hospital (2378 beds)	General surgery Neurological surgery Orthopedic surgery Urology
Boston Lying-in Hospital (138 beds)	Obstetrics
Carney Hospital (234 beds)	General surgery Obstetrics and gynecology
Children's Hospital (256 beds)	General surgery. Neurological surgery Orthopedic surgery Otolaryngology
Lahey Clinic (New England Baptist Hospital—228 beds) (New England Deaconess Hospital—310 beds)	General surgery Neurological surgery Orthopedic surgery Urology Otolaryngology
Massachusetts Eye and Ear Infirmary (227 beds)	Ophthalmology Otolaryngology
Massachusetts General Hospital (851 beds)	General surgery Neurological surgery Orthopedic surgery Urology
Massachusetts Memorial Hospitals (414 beds)	General surgery Obstetrics
Peter Bent Brigham Hospital (108 beds)	General surgery Urology
<i>Brookline</i>	
Free Hospital for Women (101 beds)	Gynecology
<i>Worcester</i>	
Memorial Hospital (185 beds)	Otolaryngology

#### CORRESPONDENCE

##### SIGNED EDITORIALS

*To the Editor:* Having read the original editorial "Pharmacology and Anesthesia" with at least marked disagreement to many of the statements in it and certainly with curiosity as to who propounded them I am prompted again to suggest the wisdom of having editorials signed.

I know that this matter has already been once disposed of in opposition and with disapproval of this procedure, but I wish again to call attention to the fact that it would have so placed the responsibility for statements which are so contrary to the opinions of experienced anesthetists that I am certain that the author would have either hesitated to make them or have prepared himself more fully to support them.

It is still my conviction that the signed editorial bears greater weight and causes less confusion and even less harm than the unsigned one, which permits statements that would frequently not be made were it necessary for the author to sign his name to it.

FRANK H. LAHEY

605 Commonwealth Avenue  
Boston 15

#### BOOK REVIEWS

*Homicide Investigation: Practical information for coroners, police officers and other investigators.* By LeMoyne Snyder, M.D. With chapters by Captain Harold Mulbar, Charles M. Wilson and C. W. Muehlberger. 8°, cloth, 287 pp., with 116 illustrations. Springfield, Illinois: Charles C Thomas, 1944. \$5.00.

The purpose of this book in the words of its author is "to make available to coroners, police officers or others, whose duty it is to inquire into the nature of a homicide, tested practical plans of procedure to follow in adequately investigating the death." He refers to it as a synopsis of factual information intended to be of practical use to men without scientific training whose duties call them to investigate potentially violent deaths.

The committee recommends a plan for the sound development of physical medicine on a lasting basis. Various subcommittees have considered the subjects of teaching, basic research, clinical research, public relations, rehabilitation, hydrology and health reports, occupational therapy and body mechanics. These subcommittees presented special reports to the central committee, and that committee has recommended an immediate program and also an eventual program. The immediate program includes the organization of the central office with a governing board and an advisory board of experts in physical medicine and related medical fields, the establishment of fellowships and residencies in physical medicine, the promotion of teaching of and research in physical medicine in all approved medical schools, the promotion of wartime and postwar rehabilitation and the provision for preparation and publication of reports of the committee. The eventual program has to do with the promotion and advancement of physical medicine through various public channels, including the adoption of certain resolutions concerning projects of organizations on which the committee looks with favor. The reports of the subcommittees are printed in full.

*Tropical Nursing; A handbook for nurses and others going abroad.* By A. L. Gregg, M.D., M.Ch., B.A.O. (Dublin), D.T.M. and H. (Lond.), L.M. (Rotunda Hosp.), member of associate staff and lecturer to nurses, Hospital for Tropical Diseases, London, and lecturer on tropical diseases, Westminster Hospital Medical School. Second edition. 16°, cloth. 185 pp. New York: Philosophical Library, 1944. \$3.00.

This small book has been written primarily for nurses in the field. There is a short chapter on personal hygiene in the tropics, followed by consideration of nursing in the various tropical diseases. There is also a chapter on the technics and special methods used in treatment. The last chapter is on the care of the eyes.

*The Treatment of Peptic Ulcer.* By George J. Heuer, M.D., professor of surgery, Cornell University Medical College and surgeon-in-chief, New York Hospital. Assisted by Cranston Holman, M.D., assistant professor of clinical surgery, Cornell University Medical College; and William A. Cooper, M.D., assistant professor of clinical surgery, Cornell University Medical College. 8°, cloth, 118 pp., with 2 charts. Philadelphia: J. B. Lippincott Company, 1944. \$3.00.

This monograph is based on the case histories of 1204 patients with gastric, duodenal or marginal ulcers admitted to the New York Hospital for various reasons. The book is divided into two parts — medical treatment and surgical treatment. There is also a chapter on the incidence of malignant neoplasms, and another gives a survey of pertinent literature, with an appended bibliography.

*Synopsis of Neuropsychiatry.* By Lowell S. Selling, M.D., Ph.D., D.P.H., director, Psychopathic Clinic, Recorder's Court, Detroit, Michigan, associate attending neuropsychiatrist, Eloise Hospital, and adjunct attending neuropsychiatrist, Harper Hospital, Detroit. 12°, cloth, 500 pp. St. Louis: The C. V. Mosby Company, 1944. \$5.00.

This simplified manual has been written for the student with the hope that it will serve him as a quick guide for diagnosis and treatment and provide a background for intensive review.

*Psychiatry and the War: A survey of the significance of psychiatry and its relation to disturbances in human behavior to help provide for the present war effort and for postwar needs.* Edited by Frank J. Sladen, M.D., physician-in-chief, Henry Ford Hospital, Detroit. 8°, cloth, 505 pp. Springfield, Illinois: Charles C Thomas, 1943. \$5.00.

This book is made up of a collection of papers presented to a conference on psychiatry at the University of Michigan. It is a survey of psychiatry and its closely allied fields. The work is divided into five parts: the philosophy of psychiatry; research in psychiatry; psychiatry in the training, experience and education of the individual; psychiatry and the war; and review of the subjects already presented, which were summarized in two symposiums.

*Infections of the Peritoneum.* By Bernard Steinberg, M.D., director, Toledo Hospital Institute of Medical Research. With a foreword by Frederick A. Collier, M.D., professor of

surgery, University of Michigan Medical School, and director, Department of Surgery, University Hospital, Ann Arbor, Michigan. 8°, cloth, 455 pp., with 45 illustrations and 21 tables. New York: Paul B. Hoeber, Incorporated, 1944. \$8.00.

This new work on peritonitis embodies the experience of the author during the last eighteen years. The work is designed for the practitioner who is confronted with the task of arriving at a diagnosis and mapping out the therapy. Most of the book is devoted to the clinical aspects of infections of the peritoneum, and many new views in the developmental mechanisms, etiology, diagnosis and treatment of peritoneal infections are included.

*Bacterial Infection: With special reference to dental practice.* By J. L. T. Appleton, D.D.S., Sc.D., professor of bacteriopathology and dean, Thomas W. Evans Museum and Dental Institute School of Dentistry, University of Pennsylvania. Third edition, thoroughly revised. 8°, cloth, 498 pp., with 86 engravings and 5 plates. Philadelphia: Lea and Febiger, 1944. \$7.00.

The primary purpose of this book is to aid the reader in forming a comprehensive concept of infection. The work is written primarily for dentists, and this third edition has been thoroughly revised and rearranged. New chapters on the ecology of the micro-organisms of the mouth, actinomycosis and osteomyelitis have been added. The work is divided into three parts: morphology, physiology and ecology of bacteria; infection; and special infections of the oral cavity.

*Principles and Practices of Inhalational Therapy.* By Alvan L. Barach, M.D., associate professor of clinical medicine, Columbia University College of Physicians and Surgeons, and assistant attending physician, Presbyterian Hospital, New York City. 8°, cloth, 315 pp., with 59 illustrations. Philadelphia: J. B. Lippincott Company, 1944. \$4.00.

This new monograph is written for physicians who wish to understand the physiologic basis, as well as the technics, of inhalation therapy. The book opens with a short chapter on the historical and physiologic background, followed by a discussion of all the diseases in which the therapeutic use of gases is indicated; it concludes with methods and apparatus used in the treatment.

*Physical Medicine in General Practice.* By William Bierman, M.D., attending physical therapist, Mount Sinai Hospital, New York City, and assistant clinical professor of therapeutics, New York University Medical College. 8°, cloth, 654 pp., with 310 illustrations and frontispiece. New York: Paul B. Hoeber, Incorporated, 1944. \$7.50.

This new textbook has been written for the practitioner in general and special fields of medicine. The work is condensed, covering all the agencies used in physical therapy and their applications to diseases of the various systems of the body. Historical references, as a rule, have been omitted, as well as extensive descriptions of the physics of light, heat and electricity.

*One Hundred and Fifty Years Service to American Health.* By Schieffelin and Company. 8°, cloth, 73 pp., with 30 illustrations and frontispiece. New York: Schieffelin and Company, 1944.

This small volume relates the interesting history of the oldest drug house in America, first founded in 1781 and still in active business in New York City, with a continuous history of one hundred and sixty-three years. The book is well done and contains a number of interesting illustrations. It is worthy of a place in all medical history collections.

*A Dynamic Era of Court Psychiatry, 1914-1944.* Edited by Agnes A. Sharp, M.A., Ph.D. 8°, paper, 149 pp., with illustrations. Chicago: The Psychiatric Institute of the Municipal Court of Chicago, 1944.

The Psychiatric Institute of the Municipal Court of Chicago was established on May 1, 1914. This small volume consists of a number of articles by the staff of the institute on the various aspects of the work of the department. The book has two functions: to record the history of the first thirty years of the institute, and to present scientific facts of court psychiatry.

*The War and Mental Health in England.* By James M. Macintosh, M.D., professor of preventive medicine, University of Glasgow. 8°, cloth, 91 pp. New York: The Commonwealth Fund, 1944. 85 cents.

This collection of nine informal essays discusses in non-technical language mental health in England during the first four years of the present war, with the outlook for the remainder of the war and the postwar period. The author considers the impact of the war on the new soldier, the industrial worker, the hospital patient and the civilian. In discussing the efforts that are being made to safeguard mental health in England the author considers such topics as hospital service and rehabilitation, and professional education. Dr. Macintosh has long been connected with the mental-hygiene movement in Great Britain, and in these essays he gives a picture of wartime conditions in England.

*Stop Worrying and Get Well.* By Edward Podolsky, M.D. 8°, cloth, 124 pp. New York City: Bernard Ackerman, Incorporated, 1944. \$2.00.

In this small book the author attempts to show how to meet daily problems in a sound way, without putting an undue strain on the mind and the nervous system. The author in a popular way discusses the effects of the mind on the body in health and disease.

*Hydronephrosis and Pyelitis (Pyelonephritis) of Pregnancy: Etiology and pathogenesis (a historical review).* By H. E. Robertson, M.D., Section on Pathologic Anatomy, Mayo Clinic, Rochester, Minnesota. 8°, cloth, 332 pp., with 11 illustrations. Philadelphia and London: W. B. Saunders Company, 1944. \$4.50.

In this historical survey the author has endeavored to present a fairly complete account of all the important work that has been done on dilatation and infection of the ureters in pregnancy. A comprehensive bibliography of 974 references is appended to the text, and all these articles are referred to throughout the work. This small book should prove a valuable reference source to all physicians interested in obstetrics and genitourinary diseases and to all libraries.

*Poliomyelitis.* By Edward C. Rosenow, M.D. Vol. A 44 of the International Bulletin for Medical Research and Public Hygiene (Editor-in-chief, W. L. Colze). 8°, paper, 87 pp., with 26 illustrations and 16 tables. New York: The International Bulletin, 1944. \$2.75.

In this pamphlet Dr. Rosenow summarizes his work on the streptococcal causation of poliomyelitis and the streptococcal source of the virus causing the disease. Dr. Rosenow states that he has succeeded in inoculating *Macacus rhesus* monkeys with his poliomyelitis virus, producing the clinical and pathologic picture of the disease, and completing twenty-seven years' work on the relation of streptococci to epidemic poliomyelitis and its virus. A summary is also given regarding treatment of the disease with antistreptococcus serum, showing that the death rate is greatly lower in patients treated with the serum. A bibliography of 115 references is appended to the text.

*Elimination Diets and the Patient's Allergies: A handbook of allergy.* By Albert H. Rowe, M.D., lecturer in medicine, University of California Medical School, San Francisco, California, and consultant in allergic diseases, Alameda County Hospital, Oakland, California. Second edition, thoroughly revised. 8°, cloth, 256 pp. Philadelphia: Lea and Febiger, 1944. \$3.50.

This new edition has been thoroughly revised, and the entire text reset. The cereal-free elimination diet has been adjusted because of the scarcity of some foods. Indications for the use of fruit-free elimination diet are discussed for the first time. A new special elimination diet for the control of colitis and various supplemental diets for obesity and diabetes food allergy, as well as special diets for infants and children, are given in detail. All menus

and recipes have been revised in the light of rationing and restriction of foods owing to the present war.

*Small Community Hospitals.* By Henry J. Southmayd, director, Division of Rural Hospitals, the Commonwealth Fund; and Geddes Smith, associate, The Commonwealth Fund. 8°, cloth, 182 pp. New York: The Commonwealth Fund, 1944. \$2.00.

This small book outlines the experience of the Commonwealth Fund during the past twenty years in the organization, construction and operation of small community hospitals in various parts of the United States. Persons interested in small hospitals in any of their aspects will find here a frank discussion of all the major questions facing such hospitals. The text lays stress on hospital administration rather than on the hospital plant. However, there is a chapter on building design, covering the broad architectural principles that have been tested in fourteen community hospitals. From an executive point of view the relations of the board of directors, the medical staff, the superintendent and the staff are discussed in sufficient detail to give the beginner a practical understanding of hospital management. In 1925, the Commonwealth Fund embarked on a definite program for the building and operation of small fifty-bed community hospitals, servicing an area of approximately twenty-five to thirty-five square miles. The fund proposed to meet two thirds of the cost of building and equipment, and the communities were to provide suitable sites, responsible management and the necessary maintenance cost. It is thus seen that aid was offered only to communities that would assume a stated share of the capital costs and would guarantee the necessary funds for maintenance and in due time become independent of foundation subsidy or supervision. Under this plan twelve hospitals have been completed, together with a county hospital built before the plan was formerly launched and an older hospital remodeled and reorganized in co-operation with the fund. The hospitals were also required to subscribe to the minimum standard for hospitals of the American College of Surgeons. This small work is aimed directly at the nonprofessional men and women who take the responsibility for the community hospital. It is written in nontechnical language and should be in every small public library in the country.

*The Principles and Practice of Ophthalmic Surgery.* By Edmund B. Spaeth, M.D., professor of ophthalmology, Graduate School of Medicine, University of Pennsylvania, attending surgeon, Wills Hospital, Philadelphia, consultant in ophthalmology, Philadelphia Hospital for the Insane, Byberry, and assistant ophthalmologist, Rush Hospital, Philadelphia. Third edition, thoroughly revised. 8°, cloth, 934 pp., with 556 engravings, containing 798 figures and 6 colored plates. Philadelphia: Lea and Febiger, 1944. \$11.00.

This third edition of a standard work has been revised by the addition of much new material and many new illustrations, thus bringing the contents fully up to date. In view of the unusual demand made on ophthalmologists by the war, emphasis has been placed on traumatic conditions. The section on muscles now includes a discussion on the physiology of squint, and the section on ptosis and its etiologic factors has been almost completely rewritten.

*A National Health Service.* By the Ministry of Health for Scotland. Reprinted. 8°, paper, 85 pp. New York: Macmillan Company, 1944. 75 cents.

This pamphlet describes and discusses the proposed comprehensive health service for England, Scotland and Wales. This plan will be put into effect on the termination of the war, and the purpose of this pamphlet is to examine the subject generally, showing what is meant by a comprehensive service and how it fits with what has been done in the past and what is being done in the present. The topics discussed include general administration, hospital and consultant service, general-practitioner service, clinic and other services, payment for the service and the application of the plan to Scotland.

*Report of the Baruch Committee on Physical Medicine.* For the Committee, by Ray Lyman Wilbur, M.D., chairman. 8°, paper, 120 pp. New York: Baruch Committee on Physical Medicine, 1944.

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## THE MECHANISM OF RENAL COMPLICATIONS IN SULFONAMIDE THERAPY

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THE ever-increasing number of case reports of renal complications in sulfonamide drug therapy indicates that neither the mechanism of their production nor the means of preventing them is yet understood. The following observations are offered in the hope that they may contribute to a better comprehension of this problem.

Early experience with sulfapyridine and sulfathiazole showed that it was mainly the insoluble acetyl derivatives of the drugs that crystallized in the urinary passages, producing obstruction and anuria. It was immediately obvious that a large urinary output would tend to keep these derivatives in solution and to prevent this complication. When sulfadiazine became available, it was predicted that the greatly increased solubility of acetylsulfadiazine in urine would be an important factor in such prevention,<sup>1</sup> but numerous reports in the literature show that this drug is by no means harmless in respect to the formation of crystals.

Various observers have described these crystalline sulfonamide deposits in the bladders, ureters, kidney pelves and tubules of patients who died of sulfonamide anuria, or who recovered when obstruction was relieved by ureteral catheterization. Similar lesions have been produced experimentally in animals by the use of large doses of the drugs.<sup>2-4</sup> When the crystalline deposits were not found in the ureters or kidney pelves at autopsy, it was assumed that they had been washed from the urinary tract before death. Gritty deposits noted on the cut surfaces—presumably within the tubules—of the kidneys of patients dying in anuria could usually not be demonstrated in microscopic sections because they had been dissolved from the tissues by the water and reagents used in preparing the sections. The finding of clefts suggesting that crystals had previously been present strengthened this belief. Subsequently various workers were able to prepare sections that demonstrated the obstructing concretions in situ in the renal tubules. It was believed that in all cases the kidney complications were due to such deposits.

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So far as can be determined, Long, Haviland, Edwards and Bliss<sup>5</sup> were the first to state that anuria in sulfonamide therapy may also be due to a true toxic injury of the kidney tubules similar to that seen in mercury bichloride poisoning. This was confirmed by Prien and Frondel,<sup>6</sup> who failed to find crystals in frozen sections of patients dying of sulfathiazole anuria. The histologic changes noted in these unobstructed kidneys were degeneration and focal necrosis of tubule cells and interstitial edema. Lederer and Rosenblatt<sup>7</sup> and Merkel and Crawford<sup>8</sup> described areas of focal necrosis in the kidneys and other organs and failed to find bacteria in these lesions; the changes in the kidneys included evidence of concretions and extensive tubular damage. Lyons<sup>9</sup> states that two types of renal complications occur—one a toxic effect on the tubules and the other a result of the precipitation of crystals. Sobin, Aronberg and Rolnick<sup>10</sup> have found focal necroses in human material that presented the clinical syndrome of sulfathiazole toxicity. Their conclusion that it has not been demonstrated that the renal changes in sulfonamide toxicity are independent of tubular obstruction by crystals seems justified.

### NONOBSTRUCTIVE SULFONAMIDE ANURIA

The two following case reports are offered as evidence that uremia and anuria may occur without obstruction of the renal tubules or urinary channels by concretions and are presumably due to a true toxic injury of the kidney tubules.†

CASE 1.† A 39-year-old man developed pneumonia and was given 10 gm. of sulfathiazole in 24 hours. The temperature fell on the day after starting chemotherapy, and he became drowsy and perspired profusely. He failed to urinate on the 2nd day after the drug was started. He was catheterized, and the 480 cc. of concentrated urine obtained showed a large trace of albumin but no crystals. For the next 4 days the patient was intermittently comatose and responsive. The temperature was normal, and the pulmonic condition showed

†I am indebted to Dr. Monroe J. Schlesinger, pathologist of the Beth Israel Hospital, who studied the biopsied tissue of these cases critically and provided fresh autopsy tissue for studies of frozen sections.

‡I am indebted to Dr. George C. Prather and Dr. Ralph Volk for permission to study and report this case.



*Sexual Anomalies and Perversions: Physical and psychological development and treatment.* By Magnus Hirschfeld, M.D., president of the World League for Sexual Reform, and director of the Institute for Sexual Research, Berlin. 8°, cloth, 630 pp. New York City: Emerson Books, Incorporated, 1944. \$4.95.

This volume comprises a summary of the works of the late Dr. Hirschfeld and is compiled as a memorial by his pupils. The book was originally published in England, and the sheets have been imported and bound in the United States to supply the American professional public. The present work was originally planned by Dr. Hirschfeld as a textbook for those who need knowledge of sexual pathology. He died before he completed his work, and his pupils finished the book and prepared it for the press. The book is divided into five parts: The physical basis of sexuality; irregular sexual development and quantitative irregularities; deflections of the sexual impulse; sexual aberrations arising from fixations on component impulses; and other partial impulses. Because of its character the volume is restricted to the medical and legal professions, to ministers and to educators and special students in the fields of psychology, biology and sociology.

*Female Endocrinology, Including Sections on the Male.* By Jacob Hoffman, M.D., demonstrator in gynecology, Jefferson Medical College, and pathologist in gynecology, Jefferson Hospital. 8°, cloth, 780 pp., with 180 illustrations. Philadelphia: W. B. Saunders Company, 1944. \$10.00.

This new treatise is divided into three parts: physiology of the endocrine glands; the clinical aspects of gonadal and reproductive endocrinology; and laboratory work. In presenting the clinical material, emphasis is placed on disturbances of functional organs. Diagnostic aids adapted for use in endocrine disorders are described. The hormonal preparations now available for the treatment of gonadal and reproductive disorders are described and tabulated, and their indications and contraindications are fully considered. Select bibliographies are attached to each chapter, and appended to the text is an index of names for all articles mentioned in the book.

*Clinics.* Vol. II: No. 5. (February 1944). Edited by George Morris Piersol, M.D., professor of medicine, Graduate School of Medicine, and professor of clinical medicine, School of Medicine, University of Pennsylvania, Philadelphia. 8°, paper, 266 pp., illustrated. Philadelphia: J. B. Lippincott Company, 1944. \$2.00.

*Simplified Diabetic Management.* By Joseph T. Beardwood, Jr., M.D., associate professor of medicine, Graduate School of Medicine, University of Pennsylvania, physician to the Presbyterian Hospital, Philadelphia, physician-in-chief to the Department of Metabolic Diseases, Abington Memorial Hospital, Abington, Pennsylvania, visiting physician in charge of diseases of metabolism, Bryn Mawr Hospital, Bryn Mawr, Pennsylvania, and chief of the Metabolic Department, Philadelphia Hospital for Contagious Diseases; and Herbert T. Kelly, M.D., associate in medicine, Graduate School of Medicine, University of Pennsylvania, associate physician, Presbyterian Hospital, Philadelphia, and chief, Department of Medicine, Doctors' Hospital, New York City. Fourth edition. 12°, cloth, 172 pp., with 7 illustrations and charts. Philadelphia: J. B. Lippincott Company, 1944. \$1.50.

This manual has been revised and brought up to date in relation to present-day conditions. Diabetic diets have been revised to conform to war and food-rationing regulations. Many of the chapters have been simplified, especially that on acidosis. There has been included a new chapter, which discusses the care of the diabetic woman during pregnancy. The manual is primarily for the diabetic patient to serve as a guide and daily source of reference.

*Manual of Urology.* By R. M. LeComte, M.D., professor of urology, Georgetown University School of Medicine. Third edition. 8°, cloth, 305 pp., with 60 illustrations. Baltimore: The Williams and Wilkins Company, 1944. \$4.00.

The third edition of this students' manual has been carefully revised and brought up to date. Emphasis has been placed on traumatic lesions, which have increased as a result

of mechanized warfare. A chapter on pain has been included, and the section on neurogenic bladder disorders has been rewritten and simplified.

*The Medical Clinics of North America.* New York Number (May, 1944). *Psychosomatic Medicine.* 8°, cloth, 262 pp., illustrated. Philadelphia and London: W. B. Saunders Company, 1944. \$3.00.

*The Medical Clinics of North America.* Mayo Clinic Number (July, 1944). *Chemotherapy.* 8°, cloth, 239 pp., illustrated. Philadelphia and London: W. B. Saunders Company, 1944. \$3.00.

## NOTICES

### BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in the Main Lecture Room of the Harvard Biological Laboratories on Wednesday, January 17, at 8 p. m.

#### PROGRAM

Transient Block of Conduction in Nerve Fibers Produced by Pressure or Ischemia. Dr. D. E. Denny-Brown.

Histochemical Reactions Associated with Basophilia and Eosinophilia in the Human Placenta. Drs. E. W. Dempsey and G. B. Wislocki.

The Argentaffin Cells of the Gastric Mucosa of Mammals. Dr. A. B. Dawson.

### GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held at the Beth Israel Hospital on Tuesday, January 23, at 8:15 p. m. Dr. Paul Klemperer, of the Mount Sinai Hospital, New York City, will read a paper "Disseminated Lupus Erythematosus and Allied Conditions." Discussion by Drs. Monroe Schlesinger, Benjamin Castleman and M. Edward MacMahon will follow.

### SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, January 16, at twelve noon. The meeting will be devoted to a nutritional film in technicolor, which will tell of the detection and treatment of nutritional diseases. This will be discussed by Drs. Tom Spies and Norman Jolliffe and others. Physicians are cordially invited to attend.

### NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

The annual meeting of the New England Ophthalmological Society will be held at the Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, on Tuesday, January 16, at 8 p. m.

Following the business meeting, which will include the election of officers, Dr. Edwin B. Dunphy will speak on the subject "Experiences in England." This will be followed by a paper "The Inheritance of Ocular Abnormalities" by Dr. R. Ruggles Gates, emeritus professor at the University of London.

### NEW ENGLAND ROENTGEN RAY SOCIETY

The next meeting of the New England Roentgen Ray Society will be held at the Harvard Club, Boston, on Friday, January 19. There will be an x-ray conference at 4:30 p. m. At 8:00 p. m., a symposium on the topic "Osteomyelitis" will be presented; Dr. Edward B. D. Neuhauser will discuss "Roentgenologic Diagnosis" and Dr. Chester S. Keefer, "Methods of Treatment."

(Notices continued on page xv)

lymphocytes and plasma cells in the focal areas. The tubules were not dilated, nor was there evidence of crystalline material or pus. A diagnosis of focal tubular necrosis of the kidney was made.

It is well recognized that renal decapsulation for the relief of anuria fails in the great majority of cases, regardless of the cause of the condition. The polyuria after operation in this case, however, was too dramatic to be explained on the basis of gradual improvement characteristic of a healing process. The apparent success of decapsulation does not constitute an unqualified endorsement for its universal use in sulfonamide anuria.

The kidney tissues removed by biopsy and the fresh kidney tissue obtained post mortem in Case I were examined for crystals in the tubules. Frozen sections were cut and the sections removed directly from the microtome knife to a glass slide without preliminary floating of the cut section in water. Some difficulty was encountered in transferring frozen sections directly to glass slides without crumpling of the tissue. By freezing the microtome knife and the glass slide just before each cut was made, presentable sections were obtained. A drop of mineral oil — in which the sulfonamides are insoluble — and a coverslip were placed over the section, which was then examined with a polarizing microscope. Tissue detail was readily observed. No crystals were present in any of the sections. The frozen sections were correlated with formalin-fixed paraffin sections. This technic had previously been successfully used to demonstrate sulfonamide crystals in kidney tubules.<sup>11</sup> By the use of this method no crystals are lost from the tissues by solution because no solvents are used at any time.

The possibility that, in Case I, crystals disappeared from the tissues after death and before frozen-section examination is also ruled out. By prior arrangement the kidneys were not washed or sponged at the autopsy table until blocks of fresh tissue had been taken for frozen sections. Furthermore, careful search of the urinary tract, from the renal papillas to the bladder, failed to reveal any crystals or concretions. In two other cases of sulfathiazole anuria with similar careful post-mortem examination, no crystals were found anywhere in the urinary tract. This is supported by the failure to find crystals in the urine of nonfatal cases of sulfathiazole oliguria.<sup>6, 12, 13</sup>

It may be argued that the crystals were washed out by the urine after they caused the kidney damage and that the changes in the kidneys were not due to the drug. A number of relevant observations have been made.

Gross, Cooper and Lewis<sup>2, 14</sup> fed large amounts of sulfapyridine to rats for several weeks and noted the results. When the rats were killed at the end of the feeding period, they showed calculi in the urinary tract in a preponderance of cases; when the animals were allowed to live for ten days after ad-

ministration of the drug was stopped, no calculi could be found, but there was dilatation of the tubules and other presumptive evidence that calculi had been present for a time. Presumably — it is so implied — it takes some time for calculi to be washed from the urinary tract after they are formed. What is most important, however, in so far as it bears on acute toxicity, is that calculi were found in the urinary tracts in *all* the rats that died during the period of drug administration.

A most instructive observation has been made by Lehr, Antopol and Churg.<sup>15</sup> They injected mice intraperitoneally with massive single doses of sulfathiazole and noted the location of its precipitation in the urinary tract. Depending on the time interval between injection and death of the animal, the precipitate was found in different parts of the tract. If death occurred within a few hours after the injection, the collecting tubules and papillary ducts were filled with a whitish material that extended into the pelves, ureters and bladder. After twenty-four hours the precipitate in the kidneys disappeared and the bladder became filled with white crystalline material that consisted almost entirely of free sulfathiazole. If the animals survived for at least several hours, anatomic signs of irritation were found in the kidneys — marked enlargement with congestion and edema. It appears that because of the extremely acute nature of the experiment these animals were able to flush their kidneys free of crystals before toxic damage to the renal epithelium produced oliguria, with resulting stagnation of crystals in the tubules.

If the findings of Gross, Cooper and Lewis are applied to the 2 clinical cases reported, it appears that both patients should have recovered spontaneously because their urinary tracts were found to be free of obstructing concretions when examined. Either obstructing crystals were never present or they were washed out before cystoscopy and biopsy were done. There is no reason to assume that the latter condition existed. After the onset of symptoms of uremia there was marked oliguria, and no crystalline precipitate was noted in the urine either before or after entry to the hospital.

If it is assumed that the areas of focal necrosis in the kidneys represent the damage done by transitory concretions, it is only logical to expect such damage to have been more pronounced in the collecting tubules<sup>2-4</sup> and, in the autopsy case, in the tubules of the renal papilla. The literature<sup>2-4</sup> records that in kidneys that contain crystalline deposits there is usually microscopic evidence of extensive tubular damage. But the tubular epithelium was intact in these locations except for the scattered foci that occurred throughout the entire kidney. The distribution of these foci did not correspond at all to the generally recognized localization of the tubular concretions. The objection that cortical biopsies do not give information on concretions located in the

evidence of resolution. He received 2000 cc. of 10 per cent dextrose solution intravenously each day, but remained anuric except for 240 cc. of urine obtained by catheter on the 9th day after starting the drug. He was admitted to the Beth Israel Hospital the next day. He had passed a rigid life-insurance examination less than a year before.

In the hospital the patient was semicomatose, but could be aroused. Examination of the chest showed evidence of a clearing pneumonic process, which was confirmed by x-ray examination. The blood pressure was 124/75. There was tenderness to palpation over the right upper quadrant but none over the costovertebral angles. There was moderate edema of the lower back and lower extremities.

Of the three catheterized urinalyses recorded, the reaction was alkaline in two, and acid in the third. The specific gravity varied from 1.016 to 1.018, and the albumin from none to a heavy trace. There was no sugar. The sediment showed a few coarsely granular and hyaline casts, 10 to 30 leukocytes and none to 12 red cells per high-power field and many bacteria but no crystals. The blood counts were normal except for leukocytosis. The blood nonprotein nitrogen was 167 mg. per 100 cc.

On the 2nd hospital day, the nonprotein nitrogen rose to 190 mg. and the blood pressure to 190/130. The carbon dioxide combining power of the blood was 38 vols. per cent, and the blood chloride 440 mg. per 100 cc. *Staphylococcus aureus* was cultured from the urine. The patient received almost constant intravenous infusions of dextrose and normal saline solution up to 5300 cc. daily, but remained anuric except for small amounts of urine obtained by catheterization.

Late on the 2nd day, cystoscopy and retrograde pyelography were done. No concretions were seen in the bladder, and no obstruction was encountered by the urethral catheters. The kidney pelves and ureters were poorly outlined in the pyelograms. It was thought that the kidney tubules were blocked by crystals, because no obstruction was demonstrated in the kidney pelves and ureters, and a rapid bilateral renal decapsulation was done under spinal anesthesia. Considerable edema was encountered in the flank muscles. The kidneys were enlarged, but the capsules were not so tense as had been expected. Tissue was taken by biopsy from the cortex of each kidney. There was no postoperative improvement, and the patient died the following day.

Microscopic examination of the biopsy specimens showed the glomeruli to be normal. The convoluted and collecting tubules were not remarkable except for small scattered focal areas of necrosis. These were represented by desquamation and breaking up of the lining epithelium of small groups of tubules, and by infiltration of a few polymorphonuclear leukocytes into these tubules. A diagnosis was made of multiple focal necroses of the kidney tubules.

**Autopsy.** The right kidney weighed 295 gm., and the left 285 gm. Both kidneys were much swollen. The remnant of the capsule stripped readily. The external surfaces were normal. The cut surface showed irregular grayish areas suggesting degeneration. The cortices measured 0.6 to 1.0 cm. in width and were sharply demarcated from the medullas, which showed similar but more marked degeneration. The calyces, pelves and ureters were normal. No crystals or concretions were present.

Microscopic examination of the kidneys showed the glomeruli to be normal except for congestion in certain areas. The capsular spaces were empty. For the most part the convoluted and collecting tubules appeared normal. Widely scattered throughout the cortex and medulla were small groups of tubules that showed cloudy swelling and desquamation. In a few places the lumens of the convoluted and collecting tubules were irregularly filled with necrotic cellular debris and granular, hyaline and cellular casts. The interstitial tissue was not increased in amount and was infiltrated, sometimes densely, with lymphocytes and plasma cells adjacent to the degenerating tubules. An occasional polymorphonuclear leukocyte was seen. In the cortex these focal areas usually appeared to be adjacent to glomeruli. The focal tubular degeneration was less marked than in the biopsy sections taken 2 days before death, which suggested that the lesions had begun to heal.

The anatomic diagnoses were as follows: bronchopneumonia of the left upper lobe; acute bronchitis; bilateral renal decapsulation; kidney biopsy wounds; arteriosclerosis of spleen; subacute passive congestion of liver; chronic duodenitis; congestion of the jejunum, ileum and stomach; subacute

diffuse pancreatitis; focal necrosis of the adrenal glands; focal tubular degeneration of the kidneys; glandular hyperplasia of the prostate gland; congestion of the bladder; and hemorrhagic urethritis.

The second case is particularly interesting because it showed a pathologic process in the kidneys similar to that of the first case and because of the dramatic improvement following renal decapsulation.

**CASE 2.\*** A 47-year-old housewife developed a temperature of 104°F. and was found to have an injected throat. Her physician gave her 20 gm. of sulfathiazole in 3 days. Her temperature was normal on the 4th day and she got out of bed. Six days later there was a recurrence of fever with sore throat. The patient received 32 gm. of sulfathiazole in 5 days. Antral puncture was done on the 6th day, and a small amount of pus was obtained. She voided little urine on this day and only 30 cc. in the next 24 hours. She was admitted to the Beth Israel Hospital.

The only significant findings on physical examination were an injected pharynx and tenderness on pressure over both kidneys, both anteriorly and posteriorly. The blood pressure was 140/80, temperature 100°F., the pulse 90, and the respirations 20.

Catheterized urines were uniformly alkaline before operation except for one specimen, which was acid; the albumin before operation varied from none to a trace. After operation the urine never showed more than a very slight trace of albumin and contained none 2 weeks later. There was no sugar. The urinary sediment before operation showed none to 20 leukocytes per high-power field but no drug crystals. The blood was normal except for a hemoglobin of 80 per cent (Sahli).

At entry the blood nonprotein nitrogen was 70 mg. per 100 cc., the carbon dioxide combining power 37 vols. per cent, the chloride 390 mg. per 100 cc., and the sulfathiazole 2.3 mg. The nonprotein nitrogen rose to 100 mg. on the next day and remained above normal until 13 days after operation. The carbon dioxide combining power remained below 40 vols. per cent until 5 days after operation. A blood culture was sterile, and urine cultures were reported as positive for *Staph. albus*.

On the 2nd hospital day, the patient received 4000 cc. of 5 per cent dextrose and of normal saline solution intravenously; the urinary output was only 45 cc. On the 3rd day, she received 50 per cent dextrose and normal saline solution, the total volume being 2200 cc., and began to show signs of peripheral and pulmonary edema. The urinary output was 15 cc. Cystoscopy was done on the 4th day and showed nothing abnormal. Both ureters were catheterized with ease, and small amounts of urine were obtained. This was followed by decapsulation of the left kidney under cyclopropane anesthesia. A biopsy from the left kidney cortex was taken at operation. The kidney was somewhat swollen, but did not bulge after decapsulation.

The effect of renal decapsulation on the fluid balance was immediate and remarkable. On a fluid intake of 2200 to 4000 cc. daily for 3 days prior to operation, the urinary output was only 45 cc. 2 days before operation and only 15 cc. on the day before it. On the 1st postoperative day it was 410 cc., and on the next day it rose to 1200 cc., climbing to a peak of 6100 cc. 8 days after operation. The intake after operation varied between 1600 and 3400 cc., with a daily average of 2500 cc.

The temperature on the day of operation reached 101°F. and thereafter fell slowly by lysis to normal. A mild pneumonic process appeared 5 days postoperatively but was of no contributory significance. An intravenous pyelogram on the 20th postoperative day showed good excretion by both kidneys within 5 minutes of injection of the dye—a normal response.

The pathological report on the tissue removed at biopsy was similar to that in Case 1. The glomeruli and most of the tubules were normal. The degenerative process in the involved tubules was slightly more diffuse and appeared to be in a later, almost healed stage. The epithelium of the tubules appeared quite intact, and there was evidence of regeneration of tubule cells. The interstitial tissue showed infiltration of

\*I am indebted to Dr. George Gilbert Smith for permission to study and report this case.

ner, the filling process progressing up the collecting tubules toward the convoluted tubules. Careful study of frozen sections in 5 cases has failed to show crystals in the collecting tubules (or higher) unless the terminal portions of these tubules were also filled with crystals. It is not necessary to assume that the pelvis or calyces must be completely filled with crystals before the tubular deposition and obstruction can occur. Such has not been found to be the case. The building up of the delta at the mouth of the Mississippi River and the progressive silting of the lower river occur despite the fact that the Gulf of Mexico has not been filled up with sediment.

The early development of this process was observed in the kidney of an elderly patient who had received sulfathiazole for a massive pneumonia.<sup>11</sup> At autopsy the calyces and pelvis of one kidney contained much crystalline material and there was a concretion blocking the ureter just above the bladder. Under the polarizing microscope acetylsulfathiazole crystals were found in the terminal portions of the collecting tubules, but there were no crystals higher in the collecting or convoluted tubules. No crystals were lost from the kidney tubules in preparation of the tissues because the previously described rigorous frozen-section waterless technic was followed.

The factor of crystal affinity is of great importance in the production of obstruction of the urinary tract. This is a surface-tension phenomenon. Crystals of the acetyl derivatives of the sulfonamides — and crystals in general — have an affinity for one another; and this causes them to adhere together to form aggregations or concretions. Anyone who has gently agitated a heavy suspension of crystals on a glass slide under the microscope and allowed the preparation to stand for a time has noted the familiar clumping of crystals.

The deposition of crystals in stagnant urine permits them to come in contact with each other to form concretions by simple aggregation. This may occur in the tubule, calyx or pelvis. Such masses of crystals then behave as ordinary urinary calculi, lodging in the kidney pelvis or the lower ureter or passing to the bladder when size permits. The readiness with which concretions form undoubtedly bears a relation to the number of crystals in the urine. The larger the volume of urine the less opportunity there is for the random collision and aggregation of crystals in suspension. If crystals are kept far apart, there is less tendency for concretions to form.

Prien and Frondel<sup>6</sup> examined the crystals in a series of 310 specimens of urine from patients receiving sulfathiazole therapeutically, and failed to find any correlation between the number of crystals in the urinary sediments and the presence or absence of evidence of renal irritation — oliguria, hematuria or albuminuria. The urines of certain

patients suffering renal toxicity showed no crystals. On the other hand, the urines of most patients with extremely heavy crystalline deposits showed no evidence of renal complication. These urines had stood at room temperature for some hours, and the crystals did not appear until the urines had cooled to room temperature.

Crystalluria, as determined by the observation of ordinary cooled urines, is probably without significance unless there is oliguria, hematuria or other evidence of renal irritation. But, as Janeway<sup>24</sup> has pointed out, the presence of numerous crystals in freshly voided urine still at body temperature is extremely significant. The urinary concentration of the drug must be rapidly decreased by forcing fluids and either reducing or withholding the drug until the crystals disappear. Further therapy must be carried on with extreme caution.

The role of urinary stasis in the causation of concretions has been shown. Crystallization is favored in stagnant water. Residual bladder urine should be eliminated, whether due to cystocele, obstruction by the prostate or urethral stricture. Bedridden patients receiving large doses of the sulfonamides should be placed on urethral catheter drainage if the residual urine exceeds 60 cc.

#### SUMMARY AND CONCLUSIONS

Renal complications to sulfonamide therapy continue to occur despite an increasing experience and the use of the more soluble sulfonamide drugs. The usual mechanism that produces these complications is the obstruction of the urinary channels by insoluble concretions composed principally of the acetyl derivatives of the drugs. Less frequently, a toxic injury of the tubules, independent of concretions, produces anuria and uremia. In such cases the only lesion in the urinary tract may be a widely disseminated focal necrosis of the kidney tubules.

Two cases of sulfathiazole anuria and uremia are reported. No obstructing concretions were encountered in the ureters or kidney pelves by cystoscopy and pyelography. Renal decapsulation was done and cortical biopsies taken. One patient died. The other recovered rapidly, apparently as a result of decapsulation. There were no crystals or concretions in the kidney tissue taken by biopsy or in the entire urinary tract (including the kidney tubules) of the fatal case that came to autopsy. A rigorous technic is described that precludes the loss of drug crystals in preparation of tissues.

The most important factor in causation of renal complications is a low urinary output.

The development of obstructing concretions depends on two physical conditions — the hydrodynamics of the urinary tract and the affinity of crystals for each other.

Crystals of the sulfonamides first form in the convoluted tubules, where reabsorption of water occurs. Sedimentation of these suspended crystals

medulla may be answered inferentially. Lack of evidence of tubular obstruction or damage of the collecting tubules in the cortex and the ready correlation of the biopsy and autopsy sections to show a consistent picture of a single lesion (focal necrosis) afford evidence that concretions were not present in the tubules of the renal pyramids.

It has been shown by numerous observers that uremic death may occur from tubular obstruction by acetylsulfathiazole concretions. It is agreed that temporary arrest of concretions in the urinary channels may produce kidney embarrassment and that such deposits may be washed out or dissolved if insufficient to produce uremic death in human beings before this clearing process is completed. But that extensive deposition of impacted crystals extending through the renal pyramids with accompanying anuria for several days will be relieved spontaneously seems doubtful.

If, in the 2 clinical cases, crystals had been present for a time only and had disappeared before the tissues were taken for study, some clinical improvement should have been manifested if the anuria was on a simple mechanical basis. It is a commonplace observation that temporary obstruction, as by a ureteral calculus, produces little kidney damage if there is no infection. The ability of the kidneys to clear themselves of crystals would be evidence of returning or surviving renal function. But in these cases the uremia became more profound with the lapse of time. It is possible that the persisting anuria was due to epithelial damage. In the absence of clinical or pathological evidence of concretions, it is reasonable to assume a primary chemotoxic cause for the focal lesions in the kidneys.

It may be objected that the changes in these kidneys were of a nonspecific nature and, together with the uremia, can be explained on the basis of toxicity due to the disease under treatment. This is unlikely. The picture is that of a transient focal degenerative process widely disseminated through the renal tubules and tending to heal without gross scar. Staphylococci were present in the urines of both patients, yet the lesions in the kidneys were not typical of such infection, nor did they suggest any other clinical condition. Furthermore, the uremia immediately followed the use of the drug. It has been produced experimentally in healthy animals by feeding sulfathiazole.

Dr. Schlesinger made an interesting observation concerning sequential relations in the biopsy and autopsy specimens. In Case 1 there appeared to be a definite progression in the degenerative and healing process, as evidenced by the sections taken at biopsy and at autopsy, two days intervening. The biopsy in Case 2 illustrates a later stage in the same healing process. The first patient received his initial dose of the drug nine days before the kidney was biopsied; the second patient received her first dose seventeen days before biopsy, or eight days

earlier. In other words, the second patient's lesion appeared to show a healing stage eight days farther along than that of the first patient. No conclusions are drawn from this observation; it is merely offered as an interesting commentary.

#### OBSTRUCTIVE SULFONAMIDE ANURIA

Although it is impossible to enlarge much on the causation of nonobstructive sulfonamide anuria beyond stating that it is probably due to a primary chemotoxic cause, much more can be said about the mechanism of the obstructive type of anuria. Prerenal factors, such as concentration of the drug in the bloodstream and excessive acetylation,<sup>16,17</sup> will not be discussed.

It is probable that crystals first form in the convoluted tubules of the kidney following concentration of urine by reabsorption of water. When deposits of insoluble acetyl derivatives are present, it is reasonable to assume that a supersaturated solution existed in situ or farther up the urinary tract. Scrutiny of the literature shows that there is no essential difference between sulfapyridine, sulfathiazole and sulfadiazine in the localization of the concretions.<sup>2, 3, 12, 18-23</sup> Furthermore, the presence of a single crystal is enough to "seed" a supersaturated solution and initiate mass crystallization. This happens in motionless solutions and is probably not strictly applicable to the urinary tract unless there is marked stasis.

The development of obstructing sulfonamide concretions from crystals in the kidneys is probably dependent on two physical conditions, the hydrodynamics of the urinary tract and the affinity of crystals for each other. The renal tubule empties its contents into the calyx in a manner analogous to the discharge of a slow-flowing river into a lake or other large body of still water. The discharge of the Mississippi River into the Gulf of Mexico provides a good analogy. Because of the disappearance of the current of the river at its mouth, suspended particles of mud and so forth are dropped, to form the well-known delta in the Gulf of Mexico. This formation builds up to such a height that the water flowing over it becomes very shallow and the fall or grade of the river becomes low. As a result, the current is slowed and deposition of suspended material occurs in the lower reaches of the river. Certain measures, such as dredging, are necessary to prevent the river from filling up and overflowing its banks.

In a similar manner the flow of urine through the renal tubule slows where the tubule empties into the broad expanse of the calyx. Not enough current remains to carry the suspended crystals onward. They are deposited in the calyx, impeding and then obstructing the flow in the terminal portions of the collecting tubules. The resulting stasis in the tubule serves to deposit more crystals. The tubules then fill with crystals in a retrograde man-

many physicians volunteered before the Procurement and Assignment Service began to function. Some local communities have suffered through unexpected deaths. The Procurement and Assignment Service has undertaken to furnish replacements wherever possible, and several thousand have been accomplished so far. Between 50,000 and 60,000 out of an estimated 140,000 active physicians in the country are enrolled in the armed services today.

But this does not tell the whole story. There were 3156 deaths among physicians in 1943. About 6000 medical students will graduate this year with the accelerated program, but the great majority will go immediately into service, leaving only the physically unfit and a few women physicians for civilian practice. These will not be enough to replace those who die. But after this year even this number will be reduced, because the Army has cut its quota of students in medical schools from 55 to 28 per cent; the Navy quota remains at 25 per cent, leaving 47 per cent to be filled by physically disabled men and by women — an almost unattainable percentage. The Selective Service regulations refuse to allow the deferment of premedical students eighteen years of age or over and the entering classes this fall will probably be reduced 25 or 30 per cent. This is perhaps the most serious situation confronting the medical profession today. If the flow of students into the schools is not maintained, certainly not enough graduates will emerge at the other end. Much pressure has been brought to bear to change this ruling, even on the President himself, but to no avail. The Army and Navy maintain that the need of young men for combat service transcends every other requirement. A bill is now pending in Congress to amend the Selective Service Act so as to allow the deferment of premedical and medical students, but it is doubtful if it will prevail. The only hope is that the war in Europe will be over shortly, thereby lessening the need for so many medical officers and allowing at least some of the older ones to return to civilian practice. This the Army has promised to do promptly.

But the medical profession has not been allowed to determine its own policy in what is perhaps the most important thing of all — medical education. The accelerated program was practically forced on the medical schools by the military leaders. It allows no time for a breathing spell between semesters for the students to rest and assimilate what they have learned or for the overworked teachers to get their second wind. The 9-9-9 program for interns and residents, set up in the face of loud protests by the leaders in our profession, scrapped overnight the carefully worked out program of graduate training calculated to furnish adequate background for the practice of medicine and for training for the various specialties.

Only about 1000 men, representing one sixth of the graduates deferred for residencies, will have the

least possible knowledge of any specialty. Of course, postgraduate instruction must be provided for these men. What form it shall take need not concern us here. Many minds and many committees are working on the problem. But what of the 3000 graduates who get only nine months of rotating internship? These men are the great source of concern at the present moment. Deplorable as the situation is, it confronts us, particularly those in hospitals not connected with medical schools. We must exert ourselves to the utmost to give these boys all they can take in nine months.

This leads naturally to certain thoughts I have in mind concerning hospitals — those of approximately 150 beds or over not connected with medical schools in the New England cities. There are about fifty of these, representing over 12,000 beds.

It is a trite remark that a hospital is an integral part of a community, and that the community should recognize its responsibility to support it. A hospital is made up of three parts — the trustees, the administration and the medical staff. No two of these can function without the third, and there should be a most cordial and sympathetic relation between the three; there should be no pulling at cross purposes. The trustees should take the staff as much as possible into their confidence; they should seek to know the various staff members and to understand their viewpoint, which is so often different from the layman's. A definite liaison should be set up between the two bodies through an intermediary unit — an executive committee, staff council or what you will. This should consist of certain members elected by the staff — not too large to be unwieldy but large enough to be representative of the various services. The director of the hospital should be an *ex officio* member. Meetings should be frequent, with a frank exchange of ideas and opinions that will prevent many unpleasant episodes that weaken the *esprit de corps* of the hospital.

I said that a community should recognize its responsibility to the hospital. Do hospitals always recognize their responsibility to their communities? This consists primarily in furnishing the best possible medical care. The first requisite for good medical care is a well-organized medical staff. This is a requirement under the minimum standard for approval as a Class A hospital set up by the American College of Surgeons. There should be a chief of staff or a chief of each service; this also is a minimum requirement. But it should be required that the Chief be given definite authority, and that he be chosen for his leadership, enthusiasm and ability to use his authority courageously and tactfully. Seniority should never be the deciding factor in his selection.

One often hears the distinction made between a teaching and a nonteaching hospital. This is wrong. Every hospital should be a teaching hospital. Someone can always be found to teach, if there are

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were excluded by law except ministers of the Gospel and divinity students. The medical profession was, however, granted a privilege accorded no other group. The Procurement and Assignment Service — made up entirely of medical men, was set up by presidential decree and given quasi-official authority, at first under the Federal Security Agency and later under the War Manpower Commission. It was charged with the voluntary procurement of enough medical officers for the armed services, selected with careful thought concerning the needs of medical schools, hospitals and civilian care. The Army and Navy agreed not to commission any doctor who was not declared available for military service by the Procurement and Assignment Service. A heavy responsibility was courageously accepted by state chairmen and local committees. They have done their work well. Medical schools have been able to retain enough of their faculty members so that the teaching has not been too much curtailed. Hospitals have been able to maintain their staffs, — much depleted, to be sure, — and the quality of service has for the most part been kept fairly normal. Many retired members have gladly resumed their former positions. Many mistakes have been made. Some communities have suffered badly, particularly in the South, where



many physicians volunteered before the Procurement and Assignment Service began to function. Some local communities have suffered through unexpected deaths. The Procurement and Assignment Service has undertaken to furnish replacements wherever possible, and several thousand have been accomplished so far. Between 50,000 and 60,000 out of an estimated 140,000 active physicians in the country are enrolled in the armed services today.

But this does not tell the whole story. There were 3156 deaths among physicians in 1943. About 6000 medical students will graduate this year with the accelerated program, but the great majority will go immediately into service, leaving only the physically unfit and a few women physicians for civilian practice. These will not be enough to replace those who die. But after this year even this number will be reduced, because the Army has cut its quota of students in medical schools from 55 to 28 per cent; the Navy quota remains at 25 per cent, leaving 47 per cent to be filled by physically disabled men and by women — an almost unattainable percentage. The Selective Service regulations refuse to allow the deferment of premedical students eighteen years of age or over and the entering classes this fall will probably be reduced 25 or 30 per cent. This is perhaps the most serious situation confronting the medical profession today. If the flow of students into the schools is not maintained, certainly not enough graduates will emerge at the other end. Much pressure has been brought to bear to change this ruling, even on the President himself, but to no avail. The Army and Navy maintain that the need of young men for combat service transcends every other requirement. A bill is now pending in Congress to amend the Selective Service Act so as to allow the deferment of premedical and medical students, but it is doubtful if it will prevail. The only hope is that the war in Europe will be over shortly, thereby lessening the need for so many medical officers and allowing at least some of the older ones to return to civilian practice. This the Army has promised to do promptly.

But the medical profession has not been allowed to determine its own policy in what is perhaps the most important thing of all — medical education. The accelerated program was practically forced on the medical schools by the military leaders. It allows no time for a breathing spell between semesters for the students to rest and assimilate what they have learned or for the overworked teachers to get their second wind. The 9-9-9 program for interns and residents, set up in the face of loud protests by the leaders in our profession, scrapped overnight the carefully worked out program of graduate training calculated to furnish adequate background for the practice of medicine and for training for the various specialties.

Only about 1000 men, representing one sixth of the graduates deferred for residencies, will have the

least possible knowledge of any specialty. Of course, postgraduate instruction must be provided for these men. What form it shall take need not concern us here. Many minds and many committees are working on the problem. But what of the 3000 graduates who get only nine months of rotating internship? These men are the great source of concern at the present moment. Deplorable as the situation is, it confronts us, particularly those in hospitals not connected with medical schools. We must exert ourselves to the utmost to give these boys all they can take in nine months.

This leads naturally to certain thoughts I have in mind concerning hospitals — those of approximately 150 beds or over not connected with medical schools in the New England cities. There are about fifty of these, representing over 12,000 beds.

It is a trite remark that a hospital is an integral part of a community, and that the community should recognize its responsibility to support it. A hospital is made up of three parts — the trustees, the administration and the medical staff. No two of these can function without the third, and there should be a most cordial and sympathetic relation between the three; there should be no pulling at cross purposes. The trustees should take the staff as much as possible into their confidence; they should seek to know the various staff members and to understand their viewpoint, which is so often different from the layman's. A definite liaison should be set up between the two bodies through an intermediary unit — an executive committee, staff council or what you will. This should consist of certain members elected by the staff — not too large to be unwieldy but large enough to be representative of the various services. The director of the hospital should be an *ex officio* member. Meetings should be frequent, with a frank exchange of ideas and opinions that will prevent many unpleasant episodes that weaken the *esprit de corps* of the hospital.

I said that a community should recognize its responsibility to the hospital. Do hospitals always recognize their responsibility to their communities? This consists primarily in furnishing the best possible medical care. The first requisite for good medical care is a well-organized medical staff. This is a requirement under the minimum standard for approval as a Class A hospital set up by the American College of Surgeons. There should be a chief of staff or a chief of each service; this also is a minimum requirement. But it should be required that the Chief be given definite authority, and that he be chosen for his leadership, enthusiasm and ability to use his authority courageously and tactfully. Seniority should never be the deciding factor in his selection.

One often hears the distinction made between a teaching and a nonteaching hospital. This is wrong. Every hospital should be a teaching hospital. Someone can always be found to teach, if there are



occurs in the terminal portions of the collecting tubules and in the renal calyx. Proximity of crystals here results in aggregation and the formation of concretions that obstruct the terminal portions of the collecting tubules. This process progresses in a retrograde manner up the collecting tubules. Calyceal concretions remain in situ or pass down the ureter much as do ordinary urinary calculi.

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## PRESIDENTIAL ADDRESS\*

### The Role of the Community Hospital in Postgraduate Teaching

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THE early meetings of this society were interrupted by World War I, and now another war disrupts its schedule. At the time of the last meeting the country was not at war, but everyone thought it soon would be. Selective service was already under way, and the Procurement and Assignment Service was in its last month of gestation. It was born in October, and then out of the blue December sky came the dastardly attack on Pearl Harbor, and war.

Through that winter and summer we had to adapt ourselves to dimouts, blackouts and air-raid alarms; the rationing of food, fuel and gasoline; the depletion and rearrangement of hospital staffs; and many other discomforts that made each approaching day uncertain and unpredictable. As the fall approached it seemed wise to the Executive Committee to postpone the prearranged meeting in Worcester. The fall of 1943 was no better, — in fact, conditions were worse, — and the meeting was again postponed. This year it was decided to chance a one-day meeting, and I am sure you will feel it has been successful.

Preparation for a world war to be fought on numerous fronts required the drafting of many millions of men from all walks of life. No groups

were excluded by law except ministers of the Gospel and divinity students. The medical profession was, however, granted a privilege accorded no other group. The Procurement and Assignment Service — made up entirely of medical men, was set up by presidential decree and given quasi-official authority, at first under the Federal Security Agency and later under the War Manpower Commission. It was charged with the voluntary procurement of enough medical officers for the armed services, selected with careful thought concerning the needs of medical schools, hospitals and civilian care. The Army and Navy agreed not to commission any doctor who was not declared available for military service by the Procurement and Assignment Service. A heavy responsibility was courageously accepted by state chairmen and local committees. They have done their work well. Medical schools have been able to retain enough of their faculty members so that the teaching has not been too much curtailed. Hospitals have been able to maintain their staffs, — much depleted, to be sure, — and the quality of service has for the most part been kept fairly normal. Many retired members have gladly resumed their former positions. Many mistakes have been made. Some communities have suffered badly, particularly in the South, where

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head, and to a lesser degree with the Cable Memorial Hospital at Ipswich.

The American Board of Surgery has set up an admirable curriculum for the training of surgeons, but the diplomats of this body will be spread out rather thin for many years to come. We of the New England Surgical Society are diplomats, but do we do all the surgery for New England? I venture to say that we do only a small fraction of it.

There are not residencies enough to accommodate all the graduates who desire to continue surgical training. Of thirty-three hospitals in New England with 200 beds or over, which might be considered large enough to furnish adequate clinical material for a resident, only nine are approved for residencies, and not all these are surgical. Most of the hospitals could provide excellent training for a resident in surgery if they would organize their staffs in some such manner as I have indicated. These hospitals represent almost 7000 beds, a fair proportion of which are assigned to surgical patients. The criticism is often raised that having a residency interferes with intern training. I do not believe that this is true. An intern should have at least eighteen months of rotating service. This will give him perhaps six months of surgery, including urology and orthopedics, but not enough to permit him to do major operating. Furthermore, the supervision and assistance a resident can give an intern is invaluable.

It is also said that a resident takes away work from the younger staff members. If the work is properly arranged this should not be so. The resident can be of great assistance with private patients, who present a field of training largely ignored in many hospitals. It is just as proper to use private patients in teaching, as it is ward patients, provided that it is done wisely. The old apprentice system certainly used private patients to good advantage. It taught the young doctor something about the art of medicine as well as about the science of medicine. How can he learn this better today than by accompanying the older surgeon on his private visits? This type of training is badly needed. So many young men know all there is to know about a given disease but nothing whatever about the personality that happens to harbor that disease.

One fault that must be overcome is the tendency for men who have been residents in hospitals in large teaching centers to feel that they must remain there indefinitely. Many must and should remain, of course — but there are certainly others who can go out into small communities to practice surgery, to their own advantage as well as that of the community. They should not do so in the expectation that they will immediately become chiefs and do

all the surgery. This thought invites disaster. They need not be ashamed to take a humble position on the staff, sell their talent to their associates, and work their way up to become leaders. Such men, if they are patient and tactful, can eventually build up a strong organization in almost any hospital. There is an immense amount of satisfaction in creative work. You who are associated with graduating residents can do much to encourage this migration.

The value of some sort of group practice has been proved beyond reasonable doubt. It is not possible to organize a private group clinic in every community; indeed, in many it may be extremely unwise. It is possible, however, to establish an informal group in many of these hospitals. If a sincere effort is made to encourage men to fill the various specialties, a reasonably complete staff can be developed. If the laboratory and x-ray setup is good and frequent consultations are encouraged, resident patients at least may have the advantage of group practice.

We should look forward to the day when all the doctors on the active staff of a hospital will have their offices in the hospital, or near enough to it for them to use its facilities easily for their ambulatory patients. This would represent a substantial economy to physicians and patients alike, in both time and money.

The need of greater supervision in surgery as well as in teaching is clear. It is so easy to master the technics of operations; it is so difficult to acquire the much more necessary surgical judgment.

You may say that I am addressing these remarks to the wrong audience. You may say that all the hospitals in which you are interested fulfill these qualifications. Be this as it may, there are many New England hospitals that are not and never have been represented in this society. Nevertheless, from time to time, either in medical meetings or in consultation service, or even in friendly association, we come in contact with some members of their staffs or boards of trustees. Should we not use such opportunities to urge the value of good staff organization? Membership in this society carries with it an implication of leadership in surgery. Twenty-seven years ago your first president, Dr. Samuel Jason Mixter, wise and sagacious leader, of whom this memorial gavel is a yearly reminder, said: "Through training of mind and hand, hospital experience under the control of able masters — these are absolute essentials and should be insisted upon in the future as they have not been in the past. It is the duty of this society to use its influence in this direction."

31 Chestnut Street

no interns — try it on the nurses. Remember teaching is like Portia's "mercy": "It is twice bless'd: It blesseth him that gives and him that takes." But teaching in a hospital requires leadership; you would not have a school without a master or a medical school without a dean. A teaching hospital will not function without a chief. Rotating services without the continuity provided by an active chief are outmoded, yet how many hospital staffs have just that, with a chief on paper?

Daily ward rounds should be regular and punctual, be conducted with decorum and be attended by all the members on service at the time. Casual rounds at all hours are demoralizing for nurses and interns alike. I know of a hospital where the visiting surgeon makes rounds whenever he chooses, and the assistant likewise. If they happen to meet, well and good; if not, assignments to operate or questions of treatment are communicated by telephone. Is it small wonder that this hospital has difficulty in getting good interns. Unfortunately, this situation can probably be duplicated many times. There should be free discussion of interesting cases at the time of the visit, not necessarily at the bedside, which may be unwise in small hospitals where gossip travels on invisible wings. The intern should be given a chance to state his views.

The minimum standard requires certain qualifications for staff membership. They are not enough. Every new member of the staff should be seen by the chief or by a staff committee and informed what his privileges as a member are at the moment and what they may be expected to be in the future. Qualifications for every step in the professional ladder should be explicitly set down in writing. It should be distinctly understood at the start that promotions are made on merit, not by seniority. If this is clearly understood when a man accepts membership on the staff and signs the bylaws, many future unpleasant episodes will be avoided. On the other hand, the younger members of the staff should not be left to their own devices, but should be encouraged to progress by special ward work, regular reading or discussions of cases.

In many hospitals, men are not restricted in their care of private patients, so that they can attempt operations or treat illnesses that they would not be allowed to do on ward service. This applies to the so-called "courtesy staff." If a man is not considered competent to undertake a ward service, he should not be allowed unrestricted privileges for his private cases. This is becoming more important with the increasing popularity of the Blue Cross and other insurance schemes, which tend to remove patients from ward service to a semiprivate status.

A well-organized staff presupposes a proper laboratory and x-ray facilities, adequate clinical records and the correct use of case-history teaching in regular clinical conferences. These conferences are of great value. If they are held at the same day and

hour each week, the habit of attendance is soon formed. If they are sporadic, the attendance will be likewise. A few full-time men, such as a pathologist, a radiologist and an anesthetist, form an excellent nucleus for such an organization. An essential part of every hospital is a good working library, with its nucleus the weekly, monthly and quarterly medical periodicals, so arranged that they can be easily consulted. The *Quarterly Cumulative Index* should occupy a prominent place. An interested staff member should be in charge as librarian, and books of reference should be carefully chosen, with due regard to the various branches of medicine. The trustees should be made to see the wisdom of setting apart adequate physical quarters for such a library, quiet and off the beaten line of travel. An intern — or a staff member, for that matter — cannot be expected to read studiously unless he is given a proper place in which to read.

It is not always realized how much this kind of setup means to a hospital. In the first place, it makes all the difference in the world in getting a quota of good interns. Even before the war there were not enough interns to go around, and naturally they chose the hospital with a reputation for good service and good training. There seems to be an underground method of communication among prospective interns. Again, the public does not realize how much this type of organization means to the community. I do not believe that the trustees realize it, or they would do more to bring it about. The more efficient hospital facilities are, the more incentive there is for young medical graduates to settle in the community. Hospital opportunities are considered a necessity today, and men look the hospital situation over carefully before deciding where to start practice. This is going to be even more so as men come back from service, having little or no idea where they want to practice.

Now all this requires tactful leadership and sympathetic co-operation; it also requires the active support of a well-informed board of trustees. Yet it is not unattainable in any of the New England hospitals.

There are small hospitals in many communities that cannot fulfill all these requirements. They cannot be expected to provide equipment for elaborate medical or surgical procedures or to furnish adequate laboratory and x-ray facilities. It is often possible for a hospital of this kind to co-operate with a neighboring, larger and better-equipped hospital, to the mutual advantage of both. Periodic laboratory and x-ray service can be furnished by the larger institution, and complicated medical or surgical cases can be transferred to it from the smaller hospital without prejudice if its staff is given appropriate appointments in the larger hospital. The Salem Hospital has an extremely satisfactory agreement of this kind with the Mary Alley Hospital of Marble-

tion of the thiochrome method of Hennessy and Cerecedo.<sup>11</sup>

### RESULTS

Data concerning the history of the 18 samples and the results of the assays are reported in Table 1, but in order to simplify the discussion of the results they will be considered under separate headings.

#### Fat

In their studies of goat's milk, Matthews and Weaver<sup>12</sup> found 7.79 per cent of fat and Holm and Webb<sup>13</sup> 6.0 per cent. Gamble, Ellis and Besley<sup>3</sup> conducted a three-year study of goat's milk and obtained an average of 3.50 per cent of fat, with a

extensive summary of data reported in the American and foreign literature, he cites a minimum content of 2.29 per cent and a maximum of 7.57 per cent.

In this study the fat content varied from 3.1 to 5.6 per cent and averaged 4.0 per cent. This value is closely similar to the 4.1 per cent reported by Asdell and Marquardt,<sup>18</sup> the 4.09 per cent reported by Turner, Ragsdale and Garrison<sup>19</sup> and the 3.50 per cent reported by Potts and Simmons.<sup>4</sup>

#### Bacteria Content

A survey of the literature revealed almost no information concerning the bacteria content of goat's milk. Gamble, Ellis and Besley<sup>3</sup> found in 728 samples from 200 to 9800 bacteria per cubic cen-

TABLE 1. Identification and Vitamin Content of Commercial Winter Goat's Milk.

SAMPLE No	No OF GOATS	KIND OF BOTTLE		FAT CONTENT	BACTERIA COUNT	HYDROGEN ION CONCENTRATION	ASCORBIC ACID	NIAICIN	PANTOTHENIC ACID	RIBO-FLAVIN	THIAMINE
		SIZE	MATERIAL	%	per cc.	pH	mg/l	mg/l	mg/l	mg/l	mg/l
1	2	1 pt	Glass	4.0	6000	6.26	1.4	1.79	3.32	1.38	0.42
2	1	1 pt	Glass	3.5	103	5.21	0.2	3.24	3.56	2.16	0.49
3	6	1 pt	Glass	4.1	100	6.35	7.4	2.44	3.52	1.15	0.50
4	3	1 pt	Glass	3.2	400	6.13	14.7	3.56	3.86	1.31	0.50
5	3	1 pt	Glass	3.1	5100	6.17	7.4	3.56	4.61	1.10	0.44
6	2	1 pt	Paper	3.3	400	6.38	8.6	2.67	6.46	1.27	0.46
7	2	1 pt	Paper	3.3	2500	6.42	7.0	2.61	2.79	1.06	0.42
8	2	1 pt	Paper	3.4	1200	6.43	9.4	2.72	3.18	1.03	0.44
9	1	1 pt	Glass	4.9	200	6.27	0.2	—	2.01	1.62	0.46
10	3	1 pt	Glass	4.6	5200	6.30	10.0	2.80	2.86	1.05	0.50
11	1	1 pt	Paper	4.6	100	6.32	9.0	3.46	2.81	1.03	0.49
12	1	1 pt	Paper	4.7	300	6.37	5.2	3.81	3.73	0.92	0.20
13	1	1 pt	Glass	5.6	800	6.62	7.6	2.93	2.59	1.51	0.50
14	1	1 pt	Glass	4.7	400	6.59	7.7	2.29	2.57	1.34	—
15	2	1 pt	Glass	4.0	400	6.55	5.6	—	2.71	1.10	0.47
16	50	1 qt	Glass	3.6	300	6.43	5.1	3.14	2.52	1.35	0.50
17	50	1 qt	Paper	3.6	200	6.42	2.0	3.15	3.22	1.27	0.49
18	6	1 pt	Glass	3.3	300	6.42	7.7	3.23	2.98	0.89	0.44
Averages				4.0	1300	6.37	6.5	2.96	3.38	1.25	0.45

peak of 5.00 per cent in February, from which time the fat content declined slowly but consistently until December. Lythgoe<sup>14</sup> found that the fat content of 36 herd samples of goat's milk varied from 2.4 to 6.8 per cent, with an average of 4.45 per cent. In assays of 439 samples of individual goat's milk the range was from 1.90 to 9.80 per cent, with an average of 4.43 per cent. Lythgoe also found a peak of 5.13 per cent in February, which was followed by a seasonal decline. In a study of 18 samples of goat's milk, Peterson, Turner and Ralston<sup>15</sup> reported a range of 2.30 to 6.50 per cent, with an average of 4.80 per cent. Besley<sup>1</sup> compared the composition of Holstein milk with combined Toggenburg and Saanen milk and reported 3.50 per cent for the latter. Ormiston and Gaines<sup>16</sup> determined the fat content of milk from eight breeds of goats and found from 4.08 per cent for Toggenburg to 6.37 per cent for Anglo-Nubian, with an average of 4.76 per cent for all breeds, but Trout<sup>17</sup> obtained less—that is, 3.54 per cent for Toggenburg, 4.41 per cent for Nubian, 4.18 per cent for Saanen and 3.84 per cent for the mixed breeds. The variation for his group of 40 samples was from 2.70 to 5.10 per cent, with an average of 3.49 per cent, but in his

timer, with an average of 775. Of these bacteria 87 per cent were *Micrococcus epidermidis*, 11 per cent were *M. aurantiacus*, and 2 per cent were *M. varians*, but none of the bacteria isolated appeared to have pathologic significance.

The bacteria count for the 18 samples of goat's milk under consideration varied from 100 to 6000 per cubic centimeter, with an average of 1300. It will be noted on reference to Table 1 that with the exception of 5 samples the bacteria count was extremely low. The average for 13 samples was 300 per cubic centimeter, a value much lower than that ordinarily obtained for cow's milk.

#### Hydrogen-Ion Concentration

In his study of the composition of 40 samples of goat's milk, Trout<sup>17</sup> obtained pH values ranging from 6.33 to 6.52. Schultz and Chandler<sup>20</sup> examined 160 samples and found that the hydrogen-ion concentration varied from pH 6.4 to 6.7. The average pH for 86 morning samples was 6.52 and for 74 evening samples 6.54, with an average of 6.53 for the total number. Gamble, Ellis and Besley<sup>3</sup> report that the pH of 4 samples of goat milk ranged from 6.54 to 6.57.

## THE VITAMIN CONTENT OF COMMERCIAL WINTER GOAT'S MILK\*

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IT HAS been estimated that the retail value of goat's milk produced in this country exceeds \$100,000,000 annually. A large portion of fluid goat's milk is used for infants, for invalids and for consumption in the home of the producer.

Various claims have been made for the superiority of goat's milk over cow's milk. Besley<sup>1</sup> states that of the two, goat's milk has larger amounts of albumin and nonprotein nitrogen, greater quantities of vitamin B<sub>1</sub>, a softer curd and smaller fat globules. Richards<sup>2</sup> reports "the fact that goat's milk is alkaline in its reaction while cow's milk is acid, a matter of the greatest importance to persons suffering from hyperacidity of the stomach." According to Gamble, Ellis and Besley,<sup>3</sup> the difference in appearance between the pigmented cow's milk fat and the colorless goat's milk fat appears to be due to a more thorough conversion of carotene to vitamin A in the latter. On the other hand, Potts and Simmons<sup>4</sup> report that analyses of milk carried out at the Bureau of Animal Industry, United States Department of Agriculture, showed no significant differences in calcium, phosphorus, iron and copper content between goat's and cow's milk. Furthermore, a review of the literature revealed relatively little information concerning the vitamin content of goat's milk. Accordingly, more information concerning its quality and vitamin potency is needed for judging its value and use, and this study was undertaken to accumulate such additional data.

### EXPERIMENTAL PROCEDURE

The samples of raw goat's milk used in this study were obtained from various localities within an area of about 100 miles from Amherst. Eighteen samples of milk were shipped to the laboratory by the producers in the usual containers, packed in cracked ice. The temperature of the milk on arrival was 32 to 40°F. The samples were examined for fat content and bacteria count within four hours after their arrival. Since the milk had been produced in widely scattered localities, it was impossible to make the vitamin assays immediately following milking, and since information was desired concerning the vitamin content of goat's milk that had been

handled under commercial conditions, it was decided to hold the milk in storage for the longest period that might occur under commercial conditions. Accordingly, after the raw milk arrived at the laboratory it was held in a commercial milk-refrigerating room until it was seven days old.

According to the owners the goats were either pure-bred or grade animals. Three breeds were represented, Nubian, Saanen and Toggenburg, the largest proportion of the goats being Toggenburg. They were all normal, healthy animals. Their ages varied for the different herds. The extreme ages were eighteen months and ten years, but the average age was about four years and, judging by the producers' reports, the animals were largely in the latter half of the lactation period. To secure data representative of the Massachusetts industry, samples of goat's milk were obtained from producers having different-sized herds. Furthermore, it will be noted from Table 1 that some samples were taken from a single animal and some were composites from several animals.

All the samples were obtained at the end of April from goats that had received a winter ration of hay and commercial grain mixtures for five or six months previously. None of them had been pastured or had received silage. The quality of the ration obviously varied with the different herds, for the hay was described as "poor quality," "alfalfa," "excellent," "local grown" and "mixed hay," and the commercial grain mixtures were of several brands and of different compositions. In addition, the goats that produced Sample 18 were given carrots and vegetable trimmings as a supplementary noon feeding.

The fat was determined by the Babcock method, and the bacteria count was made by the procedure outlined in *Standard Methods for the Examination of Dairy Products*.<sup>5</sup> A Coleman instrument was used to determine the pH value. The ascorbic acid content of the milk was determined by the method reported by Holmes, Tripp, Woelfer and Satterfield<sup>6</sup> and Tripp, Satterfield and Holmes.<sup>7</sup> The niacin was assayed by the microbiologic method of Krehl, Strong and Elvehjem.<sup>8</sup> The microbiologic procedure of Neal and Strong<sup>9</sup> was used for assaying the pantothenic acid. The riboflavin content was determined by the method reported by Holmes, Jones, Wertz and Kuzmeski,<sup>10</sup> except that potassium permanganate and hydrogen peroxide were used instead of stannous chloride and sodium hyposulfite for discharging any extraneous color. The thiamine content was determined by a modifica-

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silage. On the other hand, Peterson, Haig and Shaw<sup>32</sup> found no decrease in the riboflavin content of cow's milk that had been stored in a refrigerator for seven days.

### Thiamine

In their comparison of goat's and cow's milk, Gamble, Ellis and Besley<sup>3</sup> compared the vitamin B<sub>1</sub> potency of milk from Toggenburg and Saanen goats with that of milk from Holstein and Jersey cows. They concluded from the rate of growth of rats that goat's milk, which contained 1 international unit of vitamin B<sub>1</sub> in 4 cc. of winter milk and 3 cc. of summer milk, was richer in vitamin B<sub>1</sub> than was the Holstein and Jersey milk, which contained 1 unit in 6 to 7 cc. of winter milk and 5 cc. of summer milk. In a later paper, Besley<sup>1</sup> reported that combined Toggenburg and Saanen milk had a vitamin B<sub>1</sub> content of 28 international units per 100 gm., as compared with 16 units in Holstein milk. Williams, Cheldelin and Mitchell<sup>31</sup> found in mixed milk from Saanen, Nubian and Toggenburg goats from 0.32 to 0.48 mg. of thiamine per liter, with an average of 0.30 mg.

The thiamine content of the 18 samples of goat's milk used in this study, with the exception of Sample 12, which had a thiamine content of 0.20 mg. per liter, varied from 0.42 to 0.50 mg., with an average of 0.47 mg. This value is significantly higher than that of 0.33 mg. obtained in an earlier study of fresh milk from a herd of Ayrshire, Guernsey, Holstein, Jersey and Shorthorn cows.<sup>10</sup>

### Effect of Light

It has been frequently observed that exposure to light affects the stability of ascorbic acid, riboflavin and other vitamins. Consequently, a question may arise concerning the possible effect of light on the vitamin content of our samples of goat's milk during the week that had elapsed before they were assayed. During transit they were protected from the action of light by the packages in which they were shipped. While the samples were in the cold-storage room they were subjected to light of approximately 3-foot candles during the day, that is, eight out of twenty-four hours. Thus it seems probable that light had no significant effect on their vitamin content, even though some were shipped in glass bottles and the remainder in paper bottles. As a matter of record, however, the respective vitamin values of the 12 samples packed in glass bottles and of the 6 samples packed in paper bottles were as follows: ascorbic acid, 5.9 and 7.8 mg.; niacin, 2.92 and 3.09 mg.; pantothenic acid, 3.22 and 3.79 mg.; riboflavin, 1.40 and 1.06 mg.; and thiamine 0.48 and 0.40 mg.

### SUMMARY

Eighteen samples of goat's milk were procured from producers located within 100 miles of the

laboratory. The samples represented milk produced under routine conditions from normal healthy animals, and were shipped in the usual glass or carton containers, packed in cracked ice. The temperature on arrival was 32 to 40°F. The milk was immediately examined for fat content and bacteria count. The samples were held in a commercial milk refrigerating room until the milk was a week old and then assayed for their vitamin potency.

The average values obtained were as follows: fat,  $\pm 0$  per cent; bacteria, 1300 per cubic centimeter; hydrogen-ion concentration, pH 6.37; ascorbic acid, 6.5 mg. per liter; niacin, 2.96 mg. per liter; pantothenic acid, 3.38 mg. per liter; riboflavin, 1.25 per liter; and thiamine, 0.47 mg. per liter.

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The hydrogen-ion concentration of our samples varied from pH 6.13 for Sample 4 to pH 6.62 for Sample 13, with an average of pH 6.37. This value is somewhat lower than those cited above, possibly because the samples were a week old when examined.

### *Ascorbic Acid*

The biologic method was used in the early study of the vitamin C content of goat's milk. Hunt and Winter<sup>21</sup> fed guinea pigs 20 cc. of cow's and of goat's milk and found a somewhat larger vitamin C activity in the latter. Chakraborty<sup>22</sup> assayed the milk of cows, goats, buffaloes and human beings and found 0.009 mg. of vitamin C per cubic centimeter in goat's milk. Richmond, Grinnells and Satterfield<sup>23</sup> examined 430 samples of goat's milk and found a range of 0.5 to 2.0 mg. per 100 cc. Turner and Garrison<sup>24</sup> assayed 275 samples of morning milk from twenty-five Toggenburg goats within three hours after milking and obtained an average value of 2.0 mg. of ascorbic acid per 100 cc. Gamble, Ellis and Besley,<sup>3</sup> who assayed their samples as promptly as possible after production, obtained a range of 5.0 to 25.0 mg. per liter, with an average of 13 mg., and also observed that the spring and summer milk had more ascorbic acid than did the fall and winter milk. In a comparison of the vitamin C values of cow's, goat's, ass's, mare's and human milk, Cimmino<sup>25</sup> found that goat's milk contained 45 mg. per liter and that dehydroascorbic acid was almost entirely absent. In a study of the ascorbic acid content of Indian foods, Rudra<sup>26</sup> found that goat's milk contained 0.805 mg. per gram. Wildt and Brouwer<sup>27</sup> compared the vitamin C content of goat's and cow's milk during summer feeding on pasture and during stall feeding in winter and found no significant difference. As compared with these values, Frank<sup>28</sup> in guinea-pig assays of human, goat's and cow's milk found that human and goat's milk had practically no antiscorbutic properties. This finding was in accord with that of Meyer and Nassau,<sup>29</sup> who observed the great increase in the number of cases of infantile scurvy in Germany and made a study of the vitamin content of milk, milk powders and milk products. They found that fresh milk from goats fed green fodder was deficient in vitamin C.

The reduced ascorbic acid content of the 18 samples under consideration was extremely variable. Four samples contained almost no ascorbic acid, and the maximum content was 14.7 mg. per liter. The average value for the 18 samples was 6.5 mg. per liter, but if the 4 small and the 1 large samples are eliminated, the average becomes 7.5 mg. for the remaining 13 samples. These values are lower than those for fresh cow's milk, but they could be anticipated since Hand<sup>10</sup> has reported that the reduced ascorbic acid content of cow's milk decreased from 23 to 7 mg. per liter during six days of storage.

### *Niacin*

Apparently investigators have devoted almost no attention to the niacin potency of goat's milk, for the literature consulted contains only one report of such assays. In their study of the vitamin B content of milk from different species of animals, Williams, Cheldelin and Mitchell<sup>31</sup> included 4 samples of mixed milk from Saanen, Nubian and Toggenburg goats. They found from 2.0 to 3.2 mg. of niacin per liter, with an average of 2.5 mg.

The values obtained for the 18 samples of milk under consideration varied from 1.79 to 3.81 mg. of niacin per liter, with an average of 2.96 mg. It is of interest to compare the content of goat's and of cow's milk. Williams, Cheldelin and Mitchell<sup>31</sup> report that goat's milk contains nearly four times as much niacin as does Jersey or Guernsey milk. This relation between goat's and cow's milk is in agreement with that obtained in this laboratory in preliminary experiments.

### *Pantothenic Acid*

A review of the literature concerning goat's milk reveals only one study of its pantothenic acid content. Williams, Cheldelin and Mitchell<sup>31</sup> examined 4 samples of milk produced by Saanen, Nubian and Toggenburg goats. They obtained a minimum of 1.3 mg. per liter, a maximum of 3.2 mg. and an average of 2.4 mg.

The values obtained in this study ranged from 2.01 to 6.48 mg., with an average of 3.38 mg. In view of the paucity of data, it is hardly possible to compare the pantothenic acid content of goat's and of cow's milk, but Williams, Cheldelin and Mitchell report nearly the same value, that is, 2.9 mg. for cow's milk and 2.4 mg. for goat's milk.

### *Riboflavin*

Gamble, Ellis and Besley<sup>3</sup> compared the vitamin G (riboflavin) content of milk from Saanen and Toggenburg goats and from Holstein and Jersey cows by rat-feeding tests at different seasons of the year. They found significant differences favorable to goat's milk. Williams, Cheldelin and Mitchell<sup>31</sup> determined the riboflavin content of milk from Saanen, Nubian and Toggenburg goats. Their values ranged from 0.89 mg. to 1.2 mg. per liter, with an average of 1.1 mg.

The results obtained in this study of the riboflavin potency of goat's milk were extremely variable, ranging from 0.89 to 2.16 mg. per liter, with an average of 1.25 mg. Aside from Sample 2, which contained 2.6 mg. of riboflavin per liter, all the samples contained less riboflavin than was present in cow's milk.<sup>10</sup> The average value for the goat's milk was 1.25 mg., as compared with 1.51 mg. for raw cow's milk. It should be noted, however, that the cow's milk was fresh and the goat's milk was a week old. Moreover, as stated above, the goat ration was limited in variety and contained no grass

not to be confused with prostitution. The last-mentioned source of venereal infection has been becoming distinctly prominent in the last few years. Many authors have referred to it, and some statistics are now available. Among these is an analysis of 4641 contact reports from the Third Service Command.<sup>6</sup> Although reported by soldiers in only three eastern states, this large number of exposures took place with girls in all but nine of the forty-eight states. The pickup to whom no fee was paid was the leading source of infection (64 per cent Whites and 45 per cent Negroes), whereas the paid prostitute constituted only one fifth of the sexual contacts. This emphasizes clearly the important role played by "amateurs." Numerous other publications indicate that the fifteen to twenty age group includes the largest proportionate number of these casual female contacts. Obviously the control of juvenile delinquents is extremely difficult to handle through organized authority. Nevertheless, the public-health literature is replete at this time with reports of ambitious plans from state after state; in many instances they are being carried out with reasonable success. Organized control programs are also under way in many large cities. The juvenile delinquency problem, however, will probably not be solved until an understanding of venereal diseases is brought home to each small community; it can then reach the family unit. Not until that point is attained, will we begin to get at the root of juvenile delinquency. Taft<sup>7</sup> has outlined a seven-point program to attack delinquency, which is based on the same theory. Although he believes that the primary responsibility in meeting the problem lies with the community, it is pointed out that the federal government can do its part. Through the United States Public Health Service three things can be offered in meeting this problem: leadership, funds and trained technical consultants. The duty of the community in rehabilitating delinquents is also portrayed. The value of youth education regarding venereal diseases has been stressed by Bigelow.<sup>8</sup> The teaching of the significant facts about venereal infections in high schools and colleges is strongly advocated. This author thinks that sexual conduct is determined by ethical attitudes and standards more than by knowledge of scientific facts; consequently, an approach through the home, school, church and youth organizations should have its greatest value in developing character and standards of conduct. Nevertheless, scientific information should prevent some infections and should stimulate many persons to seek medical advice promptly when needed. A number of cities and communities have already included plans for youth education in their control programs. The British Board of Education<sup>9</sup> has issued a pamphlet on sex education in schools and youth organizations that is extremely well worked out. One in-

teresting suggestion therein is the appointment of "a really good woman physician, preferably married, youngish, with a modern approach and modern clothes" to handle the problem with girls' organizations. More comprehensive attempts are being made to reach the large Negro population in the southern states. There are also numerous reports from Canada and the Latin American countries, which are encouraging. Puerto Rico is one sadly neglected focus of venereal disease in which an organized campaign is now under way. If these programs can be managed more and more effectively, in conjunction with the admirable programs of the military services, much should be learned that will enable everyone to carry on more efficiently when peace finally arrives. An excellent paper by Ingraham and Greenbaum<sup>10</sup> emphasizes the vital part that can and should be played by the practicing physician who treats syphilis. It is pointed out that with the increase in the amount of venereal disease being privately treated, no control program can succeed without full co-operation of physicians in tracing contacts.

#### *Syphilis in Industry*

In the past numerous publications in regard to venereal diseases and industry have been quoted, and the current reports indicate continuation of efforts to work through its various branches. This has been done mainly by approaching the medical departments of large corporations. Unfortunately a relatively small percentage of industrial managements has so far been properly educated. In many plants men are still being discharged or refused work if they have syphilis, regardless of the status of their disease.<sup>11</sup> One report has been uncovered that indicates an approach through the medium of a labor organization.<sup>12</sup> The Executive Board of the California State Federation of Labor has recommended compulsory blood tests for all future members of the union in California. The co-operation of public-health facilities and the California Social Hygiene Association has been obtained. A thorough educational program is being conducted among the entire union membership. In these days of such constant bickering by some labor groups, it is pleasant to find a good word to say in their favor.

#### *Incidence of Syphilis*

Statistics for the fiscal year 1943-1944 for all the states, territories, possessions and the Panama Canal Zone are now available.<sup>13</sup> For the United States proper, 100,000 fewer cases of syphilis of all kinds were reported. In only thirteen states was there an increase, and in but four of these was it significant. These figures are compiled from the health officers' monthly statements and do not include the armed forces. Army data indicate that the rate of venereal infection has fallen below preceding peace-



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## MEDICAL PROGRESS

### SYPHILIS

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**P**ENICILLIN appears to be capable of playing as dramatic a role in the treatment of syphilis as in numerous other infections, if early indications are correct. This is the outstanding feature of progress in regard to syphilis during the past year. The incidence of this disease has been notably reduced, even without the aid of penicillin — a remarkable feat in time of war.

#### PUBLIC-HEALTH ASPECTS

In these columns six years ago it was stated that the chance of acquiring syphilis during the average lifetime was approximately 1 in 10.<sup>1</sup> Vonderlehr and Usilton<sup>2</sup> computed this 10 per cent attack rate from figures covering the years 1936 and 1937. The same authors have made a second appraisal covering the years 1939 to 1941.<sup>3</sup> Their data were obtained from the number of persons with early syphilis reporting for the first time at authorized sources of treatment that serve about 5 per cent of the population. The second survey showed that the chance of persons acquiring syphilis by the age of fifty had dropped to 1 in 15, a decrease of one third. This study clearly indicates that during the six-year period 1936-1941 the chance of acquiring syphilis dropped appreciably. These two sets of data should serve as a base line by which the control of syphilis in the future may be judged. The years covered in these surveys are those during which the campaign for the control of syphilis was being intensified. Although the decrease in the attack-rate of syphilis is indeed gratifying, it should be recalled that the United States in 1940 had not yet entered World War II. Turner<sup>4</sup> has reviewed the accomplishments

in the control of venereal diseases since 1940. His figures indicate a striking reduction in the level of days lost per man per year because of venereal diseases in the armed forces. In 1940, as many as 1278 days were lost per 1000 men per year, whereas at the time of Turner's writing (1943) the rate was 368 days per 1000 men per year. He credits most of this magnificent accomplishment to the work of venereal-disease control officers who were assigned to camps and to all theaters of operations. This is an example of intelligent utilization of specially qualified medical personnel. Turner believes that a civilian program designed to control venereal diseases should be similarly built around medical specialists in this field. The tasks that lie ahead of the military in respect to venereal diseases are outlined. A public-health step of first importance has been taken by Congress.<sup>5</sup> A new law abolishes all punishment for venereal disease in the armed forces, provided only that the infected person complies with Army or Navy regulations requiring him to report and receive appropriate treatment. Failure to report a venereal infection remains punishable by court-martial or other disciplinary action. This measure recognizes that fear of punishment does not prevent exposure but does promote concealment and self-treatment.

#### *Juvenile Delinquency*

Turner<sup>4</sup> also stresses the expansion of educational efforts, particularly those directed to the young women of the community, the maintenance of the gains made against organized prostitution and the problem of the sexually delinquent girl, which is

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considered adequate therapy. It poses the question whether the correct definition of adequate therapy is actually known.

Six cases of acute encephalopathy were encountered by Young and Gordon.<sup>25</sup> These patients were being treated with a heavy-dosage, multiple-syringe, intensive schedule. All received the conventional therapy for hemorrhagic encephalitis, but only one patient recovered. The clinical pictures and autopsy reports are given. Typical necropsy findings were edema and numerous petechial hemorrhages of the entire brain, slightly larger hemorrhages in the pituitary gland, cloudy swelling of the liver and congestion of the kidneys and alimentary canal. This particular reference is quoted to emphasize one of the grave disasters that may be encountered in massive-treatment programs. A distressingly high percentage of all types of treatment reactions is still being observed, even with the modified intensive schedules that are in general use in military stations, governmental treatment centers and many large civilian hospitals. All this work must still be considered experimental, as has been repeatedly emphasized in the past. Any physician treating syphilis is frequently besieged by his more alert patients with inquiries about, or demands for, rapid treatment. It is unfortunate that the lay press is so prone to publicize experimental medicine.

## DIAGNOSIS

### *Serologic Tests*

In an editorial, "The Serology Was Positive," Moore<sup>26</sup> makes a plea for a correct usage of terminology. He points out that "serology" is a branch of science and not a test. It is a term that cannot be limited to diagnostic tests for syphilis, nor can serology be expressed as "positive" or "negative." It is pointed out that the correct expression is "the serologic test was positive." Moore goes on to call attention to the fact that the adjective "serologic" is not applicable to spinal fluid tests, as this fluid is not a serum. It may be added that a commonly accepted abbreviation for the term "serologic tests for syphilis" is "STS." This will be seen in much of the literature pertaining to syphilis at the present time. It is always correct, in addition, to name the actual test employed, if one so desires.

For several years the Kahn verification test has been employed in some laboratories in an attempt to detect false positive tests in routine serologic practice. Kahn<sup>27</sup> has continued his work with this special test and has introduced improvements. He has determined differential characteristics of specific and nonspecific serologic reactions with different temperature and electrolyte requirements. These procedures "type" serodiagnostic reactions on the basis of their specificity. The verification test may give cases that are free

from clinical indications of syphilis. If nonspecific type reactions are found in the absence of any history or clinical evidence of syphilis, Kahn believes that the positive reactions are nonspecific and syphilis can be ruled out. This is certainly a step in the right direction. If this work is corroborated, and if the verification test becomes widely available, it should be of considerable value.

An English Navy innovation has been reported by Crick,<sup>28</sup> who recommends the use of serologic precipitation tests for syphilis aboard large ships in wartime. This procedure has proved of value in dark-field-negative lesions and suspicious eruptions. It has also relieved the hospital ships in routine blood examinations. It is not advocated to the exclusion of hospital laboratory tests, but is recommended as an adjunct in certain circumstances.

### *False Positive Tests*

An analysis has been made by Kolmer<sup>29</sup> of the results of nine serologic surveys from 1935 through 1941. A large number of the false positive reactions in the serodiagnosis of syphilis were found to have been due to errors in the collection of blood, resulting in excessive contamination or hemolysis, and to faulty laboratory technic. Technical errors inherent in the tests themselves may give false indications even in skilled hands. Comparing the results of these various serologic surveys with another in 1943, Kolmer found an appreciable decrease in the percentage of false positive reactions in serums of normal nonsyphilitic individuals. The author classifies the diseases and conditions known or suspected of causing biologic false doubtful and positive reactions into three groups. First, a variable incidence is seen in yaws, pinta, leprosy, malaria, vaccinia and vaccinoid, infectious mononucleosis and virus pneumonia. A second group of ten febrile diseases is stated to show an unknown incidence. A still larger third group of conditions is mentioned in which the evidence regarding false positive tests is not conclusive. A listing of these two latter groups will be omitted to avoid confusion; it is suggested that suspected false positive reactions occurring in diseases other than Kolmer's first group be subjected to exacting scrutiny. In Kolmer's paper it is stressed that the entire responsibility of the diagnosis of syphilis should not be placed on the laboratory findings and that there is no substitute for thorough clinical examination. In cases in which the reactions are persistently positive it is frequently advisable to make a tentative diagnosis of syphilis and institute treatment. This is particularly true if the positive reports come from more than one laboratory and by multiple technics. A situation such as pregnancy is an additional indication for treatment.

It seems apropos at this point to enumerate a few suggestions for the prevention of hemolysis of blood specimens. The syringe and needle used to draw blood should be dry and sterile. Alkalies and other

time levels and is less than half that recorded during World War I.<sup>14</sup> If this trend continues, it will be the first war in history during which syphilis has been held in check. This applies to the general public and even more remarkably to the military services.

### EXPERIMENTAL STUDIES

Further studies of *Treponema pallidum* by the electron microscope are available. Mudd, Plevitzky and Anderson<sup>15</sup> have compared several strains with other spirochetes and confirmed the findings of previous students. Cares<sup>16</sup> has reported on the differential motility characteristics of *T. pallidum*. His material was obtained from infectious lesions rather than from cultures. Three other forms of spirochetes were encountered. The identifying motility types of locomotion and changes in shape are carefully described. Although this work was done with the use of the electron microscope, a good deal of the motility of *T. pallidum* can be observed with an ordinary microscope. A review of this article should be beneficial to any practitioner capable of and equipped to do dark-field examinations.

An interesting study has been reported regarding the effect of fever on the distribution of arsenic in the tissues of rabbits injected intravenously with Mapharsen.<sup>17</sup> It was found that there were distinctly higher concentrations of arsenic in the tissues of rabbits treated with Mapharsen and fever than when the former was given alone. Observations made twenty-four hours after treatment revealed that significant amounts of arsenic were still present in all the tissues in the fever-treated group; whereas in the group receiving Mapharsen without fever only negligible amounts of arsenic could be detected in tissues other than the kidneys and lungs. These findings suggest that fever may either bring about an increased deposition of the drug in the tissues or fix it more firmly, thus delaying elimination. Both factors may of course be involved. These observations may explain the enhanced therapeutic action of arsenical drugs when combined with fever, and perhaps also the increase in toxic reactions.

Many reports have appeared in recent years regarding the use of ascorbic acid as a detoxifying agent during treatment with intravenous arsenical compounds. During the last year several publications have appeared on detoxication by means of *p*-aminobenzoic acid. Sandground<sup>18,19</sup> carried out extensive experiments with rats. Massive acutely poisonous doses of several pentavalent arsenical drugs were used. The survival rate among rats that received *p*-aminobenzoic acid compared with that of controls was so high that its protective role seemed established beyond question. Furthermore, there appeared to be no inhibition of the trypanocidal action of the arsenic. Subsequently, Sandground and Hamilton<sup>20</sup> carried out parallel experiments

with lethal doses of neoarsphenamine and found the protective capacity of *p*-aminobenzoic acid equally effective. The clinical implications of these findings, especially with respect to the intensive treatment of syphilis, seemed promising, but when this work was applied clinically, the results were discouraging.<sup>21</sup> A small group of patients with neurosyphilis were given *p*-aminobenzoic acid in conjunction with pentavalent arsenical compounds. Such oral administration, however, did not prevent nitritoid crises, gastrointestinal reactions or optic-nerve damage. This apparent failure may not be as disheartening as it sounds, and one can still hope for more satisfactory results with further work. Another group of investigators,<sup>22</sup> studying the detoxifying actions of several organic acids, confirmed Sandground's findings in experiments on animals. It was further observed that the effect is most favorable when the arsenical and the protective agent are injected intravenously in the same solution.

### PATHOLOGY

Although comparatively little medical literature has been available from Germany in recent years, one quite interesting report has turned up. Gottschalk<sup>23</sup> quoted the Magdeburg combined morbidity statistics for the period 1928-1936 regarding venereal diseases as a cause of death. These statistics include 8182 deaths for which both the clinically determined cause of death and autopsy findings were available. Of this number 322 (3.9 per cent) died of disease that was clinically diagnosed as syphilis, and in 214 of these (66 per cent) the clinical diagnosis was confirmed by autopsy findings. Another 192 cases were found in which the autopsy determined syphilis to be the cause of death, bringing the total number to 406 cases of death due to syphilis. By means of autopsy, therefore, 26 per cent more cases were diagnosed in which death was due to syphilis than by clinical findings alone. Aneurysm and tabes dorsalis were the two syphilitic conditions most frequently incorrectly diagnosed clinically. Black-Schaffer and Rosahn<sup>24</sup> report a continuation of their study of autopsy reports from Yale University School of Medicine. An attempt was made to correlate the serologic tests for syphilis in 313 autopsies on syphilitic patients. Serologic positivity was significantly more frequently associated with anatomic lesions of syphilis than was serologic negativity. Analysis of the data from numerous standpoints suggested that increasing activity of the disease is associated with an increasing frequency of positive blood tests. The likelihood of syphilis being the primary cause of death was more than twice as great in patients with positive serologic tests than in syphilitics with negative tests. These findings are quite interesting in view of a strong tendency among syphilologists to disregard the so-called "serofast status," which not infrequently persists in late syphilis even after what is

penile lesions observed by Loveman and Morrow.<sup>39</sup> The urethral discharge in these cases should be serosanguineous or seromucoid, as contrasted to the thick purulent discharge seen in gonorrhea. Mild symptoms of obstruction to the flow of urine may be present. Here again, painless indurated nodules should be palpable. Dark-field examination from the discharge or from the regional lymph nodes should be positive.

### *Lymph-Node Puncture*

Loveman and Morrow,<sup>40</sup> have also stressed the value of dark-field examination of lymph nodes in the diagnosis of early syphilis. Twenty-three of 25 cases of early syphilis yielded positive findings by this method. In 12 (60 per cent) of 20 cases dark-field examination from the local lesions resulted in negative findings. A general discussion of technic is given. Agee<sup>41</sup> writes in a similar vein and points out the value of lymph-node puncture in patients whose satellite nodes persist after the healing of the primary lesion. He has found positive dark-field examinations after as much as eight weeks' intensive therapy. This might arouse speculation regarding the value of one of the commonly used criteria of the effectiveness of early treatment. The rapidity with which surface lesions become dark-field negative under various forms of treatment is stressed as an indication of the effectiveness of therapy. Agee's article indicates that viable organisms may be found in lymph nodes after many weeks of intensive treatment. This should stimulate more thought and conservatism in acclaiming the value of intensive therapy. Twenty years from now we may be disappointed in present-day methods, including the magic of penicillin. There may be more value than we realize in prolonged courses of treatment for syphilis.

### *Bone Syphilis*

Francis and Kampmeier<sup>42</sup> have reported an interesting study of bone lesions found in late acquired syphilis. Roentgenographic evidence of the disease was found in one hundred and seventeen bones in a series of 67 patients. The order of frequency of the most usual sites of bone involvement was as follows: tibia (29 per cent), clavicle, skull, fibula and femur. Lesions were found in twenty different bones. The pathologic findings of tertiary syphilis of the bone are described. In the series reported, periostitis, gummatous osteitis and sclerosing osteitis were found. The amount of bone syphilis reported by these men is much greater than is commonly observed. It must be remembered, however, that they were seeking this one feature by routine x-ray studies rather than by clinical means.

### *Syphilis of Stomach*

Although syphilis seldom produces gastric lesions, it is a diagnosis that may be easily missed. Cunha<sup>43</sup>

has recently published his observations on this topic. He believes that a positive serologic test in a patient with gastric deformity demonstrated by x-ray calls for an immediate re-evaluation of the gastric diagnosis. It is pointed out that there is no reason why a syphilitic patient cannot have a malignant neoplasm and that a benign ulcer can also occur in a syphilitic person. Diagnostic features that point toward syphilis of the stomach are outlined as follows: an unduly long history of illness, comparatively mild anemia, higher free-acid values than usual, the absence of gross and occult blood, and extensive tissue involvement as seen by x-ray. Cunha has observed 9 cases of syphilis of the stomach.

### *Syphilis of Liver*

An excellent study of syphilis of the liver has been reported by Hahn.<sup>44</sup> His data on 1165 adult syphilitic patients were obtained from autopsy material at the Johns Hopkins Hospital over a period of nearly thirty years. He found no autopsy report of early syphilis of the liver. The incidence of late syphilis of the liver among the syphilitic patients was 4.9 per cent. The most outstanding pathological finding was the focal gummatous nature of late hepatic syphilis. An analysis of the clinical findings, verified by pathological reports, revealed that no single manifestation was constantly or even usually present. Abdominal pain seemed to be the most significant subjective complaint. The most frequent physical finding was a palpable liver. The spleen was also palpable in many cases. The blood was seropositive in 81 per cent of the patients. Not one patient with late syphilis of the liver had received adequate therapy for early syphilis. The median estimated duration of syphilis was fifteen years. The correct hepatic diagnosis had been suggested in only 12 per cent of the total. Portal cirrhosis and carcinoma of the liver accounted for over 50 per cent of the erroneous diagnoses. It was found that hepatic syphilis rarely produces ascites, huge livers, pronounced weight loss, high septic fever or severe toxemia. There was no evidence that liver damage due to syphilis predisposed to hepatic injury from arsenicals. Portal cirrhosis rarely occurred in association with definite hepatic syphilis. This is a thorough study that merits careful scrutiny by internists as well as physicians in general practice, even if they have no interest in or do not treat syphilis.

### *Cardiovascular Syphilis*

More publications than usual have appeared on the various phases of this topic during the past year. Many are of general interest, whereas others seem to be of value mainly to cardiologists, who deal with the obtuse facets of cardiovascular disease.

Mattman and Moore<sup>45</sup> point out that, although uncomplicated syphilitic aortitis is often an asymptomatic

chemicals should be avoided if syringes are boiled. Blood should never be sprayed through the needle into the tube; the needle should be detached, and the blood should be expelled slowly against the side-wall of the tube. The tube should be placed in a cold place at once, preferably in a refrigerator, especially in warm weather, and should be kept there until mailed. These procedures will help to reduce the number of anticomplementary specimens.

In previous progress reports, references to false positive tests after smallpox vaccination have been quoted. Further confirmation of this observation has been published by Favorite.<sup>30</sup> A group of 202 medical students and nurses known to have negative serologic tests were vaccinated and repeatedly tested, using three technics. Twenty-four persons (11.8 per cent) were seropositive at some time following the vaccination. These cases were retested every two weeks. There was a gradual diminution of reactions, with all becoming negative by the end of one hundred and twenty days.

A group of investigators at the Iowa State Laboratory<sup>31</sup> studied the reactions in the serums of 993 known syphilitic persons by three technics. It was found that 13.5 per cent gave entirely negative reactions for all three tests and that 9.7 per cent gave contradictory reactions. It is a frequent observation that these contradictory reactions may persist or may disappear, with or without antisyphilitic treatment. These authors offered several explanations for the disappearance of contradictory reactions. It is stated that they may be due to the development of a latent nonreacting stage of the disease, to a spontaneous cure or to causes other than syphilis that cease to exist. The authors think that the last explanation is the most probable and cite a number of cases to substantiate their belief. This spontaneous reversal to a negative state may require a period of weeks or months. It is again stressed that physicians should not base their diagnoses solely on serologic reports.

The responsibility of ruling out syphilis is equal in importance to that of diagnosing it. Taussig<sup>32</sup> reports in this vein and quotes illustrative cases. He offers a list of suggestions to avoid errors in diagnosis in patients who show no other evidence of syphilis than a repeatedly positive serologic test. One point to bear in mind is the fact that serums positive with less sensitive technics, such as the standard Wassermann test, but negative with highly sensitive tests are probably not syphilitic. An instance of false positive serologic tests for syphilis in several members of a family has been reported.<sup>33</sup>

It is quite universally accepted that cerebrospinal fluids are much less likely to yield false positive reactions. This may indicate that the reagin-like substances that are thought to occur in the blood serums of nonsyphilitic persons yielding false positive reactions do not occur in cerebrospinal fluids.

An article has appeared, however, reporting 8 cases with false positive spinal-fluid Wassermann reactions.<sup>34</sup> Seven of these occurred during the course of meningitis. In 5 cases two different organisms were cultured from the spinal fluid; 2 were aseptic. In 7 of the cases the blood was seronegative.

## CLINICAL PROBLEMS

### *Early Syphilis*

An interesting study of 2451 newly inducted soldiers revealed a surprising amount of syphilis.<sup>35</sup> All had been classified 1-A by an induction board and were presumably free of venereal disease. Fifty-five men were found to be definitely syphilitic: 4 had early syphilis; 8, neurosyphilis; and 43, latent syphilis. An additional 61 men were thought to have had previous syphilitic infection and to have been cured by treatment. Only the 4 men with early infection showed physical evidence of the disease, and only 10 of the others had a doubtful or positive serologic test. This indicates the importance of an adequate history in conjunction with serologic testing and physical examination. A good discussion of the principles of diagnosis in syphilis and the comparative merits of available procedures has been given by Barnett.<sup>36</sup> The importance of meticulous examination is stressed. The ease with which minor bits of clinical evidence may be overlooked is well illustrated.

As in many other diseases, the failure to make a diagnosis of syphilis may often be due simply to not thinking of its possibility. Bearing the disease in mind is of utmost importance with early lesions in the seronegative stage. An interesting commentary on this point has been published by Spatz.<sup>37</sup> This author reports a series of 11 consecutive cases of primary syphilis in which only 3 presented the classic type of painless, hard, solitary chancre. The lesions in the remaining cases resembled the ordinary chancroidal or balanitic ulcerations; they were not indurated, often were multiple and sometimes were painful. All these cases were diagnosed by dark-field examination. The question is brought up how many latent or advanced cases of syphilis were not detected in their early stages simply because the primary lesions were so atypical or minor as not even to suggest syphilis to the examiner. Each and every case with a genital ulcer of any description should be subjected to dark-field examination. This applies likewise to many lip and mouth lesions.

The misleading appearance of a meatal chancre has been stressed by McCarthy.<sup>38</sup> It often suggests a mild or recurrent gonorrhea. In the earliest stages it may even appear to be an abortive herpes genitalis. Induration eventually becomes evident, however, and is a sign of utmost diagnostic importance. If the possibility that the lesion is syphilitic is recognized, the problem should be simple. Intraurethral chancres occurred in 8 (11 per cent) of 70 patients with

types. Aring<sup>54</sup> has also written on acute syphilitic meningitis. He is in general agreement with the preceding author and stresses the importance of intensive therapy. It is pointed out that tryparsamide or fever therapy may be required in some cases.

Syphilis of the spinal cord is discussed at considerable length by Adams and Merritt.<sup>55</sup> These authors classify and discuss spinal syphilis based on pathologic changes. They point out that a pure form of spinal syphilis without lesions of the brain is exceptional, and state that the basic pathologic lesion is probably chronic inflammation of the spinal meninges. Almost every conceivable cord disease may be simulated clinically by spinal syphilis. The authors believe that the introduction of any foreign substance intrathecally, whether a spinal anesthetic or arsphenamized serum, in a patient who has neurosyphilis is dangerous. The clinical results in the treatment of spinal neurosyphilis are discouraging.

The Medical Corps of the Army has set up a special program for the management of neurosyphilis.<sup>56</sup> Certain general hospitals are designated as treatment centers, and all cases diagnosed as neurosyphilis are transferred there for diagnostic review and treatment. It is expected that the bulk of cases will be asymptomatic, with minor spinal-fluid changes, will respond relatively quickly to therapy and will be retained in military service. All other cases will be separated from the service after optimum treatment. Thereafter the United States Public Health Service will maintain observation and treatment as indicated.

(To be concluded)

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matic disease, the extent to which this is true varies not only with the skill and diligence of the clinician but also with the extent of pathologic damage to the aorta. These authors compare two groups of patients observed at the Johns Hopkins Hospital. In a series of 105 patients found at necropsy to have uncomplicated syphilitic aortitis, the clinical diagnosis had been correctly made or suspected before death in only 41 per cent. The authors then add an additional series of 79 patients, observed ten years later, in which the incidence of correct clinical diagnoses had increased to 68 per cent. This appears to indicate that Moore's criteria for the clinical diagnosis of uncomplicated syphilitic aortitis are valid. A keener appreciation of them will, of course, increase the percentage of accurate diagnoses. Hypertension, extensive arteriosclerosis and rheumatic heart disease must, if possible, be ruled out. Moore emphasizes the following symptoms and signs in the diagnosis of syphilitic aortitis: roentgenologic demonstration of dilatation of the first portion of the aorta; heart failure or lowered cardiac reserve in the absence of other causes; localized substernal pain (to be differentiated from anginal pain); and characteristic changes in the aortic second sound. Dressler and Silverman<sup>46</sup> write in a similar vein on the same topic. The interesting feature of their report is the finding of syphilitic aortitis in 8 of 50 cases of congenital syphilis. It is their belief that this condition is more frequent in congenital syphilis than has heretofore been held.

Jones and Bedford<sup>47</sup> describe a series of 103 syphilitic patients subject to paroxysmal pain in the chest that was investigated with special regard to its clinical characteristics. The average period between infection and the onset of pain was twenty-four years. The clinical findings included varying degrees of dilatation of the aorta, cardiac enlargement, aortic incompetence and essential hypertension. Seventy-six patients suffered angina on effort, and 64 had pain apart from effort. Nocturnal attacks were of common occurrence and were usually independent of paroxysmal dyspnea. Symptoms of coronary thrombosis not attributed to syphilis occurred in 10 cases. Post-mortem findings are reported on 12 cases. Pathologic evidence that uncomplicated aortitis causes anginal pain was lacking. Stenosis or occlusion of the coronary ostia was usually found in conjunction with typical syphilitic lesions, but it is stated that atheromatous and thrombotic coronary occlusion may be coincident with syphilis of the aorta. These authors do not believe that an atypical or pseudoanginal syndrome due to syphilitic aortitis exists.

It is stated by Arkin<sup>48</sup> that syphilis is responsible for about 20 per cent of the cases of chronic cardiac disease in adults. This author stresses the preventable nature of syphilitic heart disease, and estimates that early diagnosis and adequate treatment should prevent at least 90 per cent of cases of cardiovascular

syphilis. He stresses the need for a periodic physical examination and roentgenographic study of every patient with evidence of syphilis. Arkin's criteria for the diagnosis of uncomplicated aortitis are slightly more elaborate than those of Mattman and Moore.<sup>45</sup> Aortic insufficiency is discussed at some length by Hammon.<sup>49</sup> Syphilitic aortic insufficiency is one of the eight groups into which this author divides these cases. He points out that repeatedly negative serologic reactions occur in from 10 to 15 per cent of cases of syphilitic aortitis. The clinical diagnosis is elaborated in some detail, and the author describes several interesting cases in which syphilis was a factor of the incorrect diagnosis.

Jones and Bedford<sup>47</sup> found abnormal cardiograms in 57 of 94 syphilitic patients subject to paroxysmal pain in the chest. Cole and Bohning<sup>50</sup> paid special attention to electrocardiographic patterns in cardiovascular syphilis. They have correlated the post-mortem findings and electrocardiograms in 30 cases. No specific pattern was found to be pathognomonic of syphilitic cardiovascular disease, but there were 11 cases of left ventricular preponderance and 3 cases with an anterior-wall infarction pattern. These seemed frequently due in whole or in part to syphilis. Parsonnet and Bernstein<sup>51</sup> wrote on the same topic. They consider the electrocardiogram of vital importance as a diagnostic, prognostic and therapeutic guide in cardiovascular syphilis, but state that a diagnosis cannot be made from it alone. They also point out that some of the methods of treatment are factors in initiating cardiographic changes that are indicative of myocardial damage.

### *Neurosyphilis*

O'Leary and his associates<sup>52</sup> have published an excellent analysis of the spinal-fluid findings in asymptomatic neurosyphilis. A general classification of spinal fluids is given in tabular form, according to the degree of abnormality observed in each of the five usual tests. Thus the character of the impending nervous-system involvement may be anticipated and the progress of the disease and the effect of treatment may be properly estimated. It is stated that if the spinal fluid is still negative by the fourth year of the disease, neurosyphilis will probably not develop.

Although acute syphilitic meningitis is a comparatively uncommon complication of syphilis, 15 cases are reported by Skogland.<sup>53</sup> It is pointed out that acute meningitis usually occurs in early syphilis and in untreated or inadequately treated patients. The author states that the blood Wassermann reaction is negative in approximately a third of the cases. Three clinical pictures may be seen: acute hydrocephalus, acute meningitis of the vertex and acute basilar meningitis. Recovery is usually prompt with proper treatment, trivalent arsenic being the initial choice, but sequelae may occur. The author's cases illustrated the three different



Dr. Holmes has just arrived and I need him. Since time is short, I shall put it up to him this way. If you glance at the first paragraph in the abstract you will see that for twelve years this woman was apparently coughing up purulent sputum, which for a year had often been bloody. She raised as much as a cupful; it smelled bad but later it states that x-ray examination was negative.

DR. GEORGE W. HOLMES: That is correct.

DR. MEANS: I have a case of tuberculosis in mind in which the x-ray films were reported to be negative for tuberculosis.

DR. HOLMES: That is unusual. About the only time when x-ray films are negative in pulmonary tuberculosis is when the lesion is in the bronchus. You can have an ulcerating lesion in the bronchus with tubercle bacilli in the sputum and a negative x-ray film. You cannot have parenchymal tuberculosis and a negative x-ray film.

DR. MEANS: One of the wisest men on diseases of the chest, under whom I was fortunate enough to be a student, was the late Dr. Frederick T. Lord. He said that any patient who had a story of this sort must have a chronic bronchopulmonary suppurative process of some kind. If not in the lung, at least in the bronchus.

DR. HOLMES: Do not let me mislead you. The fact that the x-ray films are negative does not prove that the patient did not have a lesion in the bronchus.

DR. MEANS: I know that very well. The answer is that the radiologist cannot necessarily determine a lesion of the bronchus.

According to Dr. Lord's philosophy, if I remember it correctly, this woman ought to have a chronic lung abscess or bronchiectasis. It is too long a history for abscess, however. A lung abscess would have cleared up or would have killed her by that time; therefore it must be bronchiectasis. Dr. Holmes could not demonstrate bronchiectasis, I suppose, if the cavities were empty. Is that correct?

DR. HOLMES: We miss a certain number of cases but this woman's chest is entirely normal. I hardly think that she could have had bronchiectasis.

DR. MEANS: How could she have raised a cupful of foul-smelling sputum daily for twelve years and not have had anything in the chest? Had she a fistulous tract that fed pus into the bronchus from somewhere else?

DR. HOLMES: We do not know whether the observation was accurate. The material may have come from the stomach.

DR. MEANS: The gastrointestinal tract was reported negative by x-ray study.

DR. HOLMES: The x-ray films do show a large liver.

DR. MEANS: I am going to get to that. Let us stick to the thorax for the moment. I was thinking about the esophagus and the bronchus. Are they mixed up with one another or connected in some unholy alliance?

DR. HOLMES: If they are, we have no evidence of it.

DR. MEANS: She was said to have vomited blood and, unless it is a perfectly erroneous history, I am forced to conclude, x-ray or no x-ray, that she either had or had had some sort of chronic bronchopulmonary suppurative process. I do not believe that these facts fit with any other interpretation, and a little thing like a negative x-ray should not shake one in one's argument if one thinks that the premises are sound. We are told that she was vomiting. If this was all gastrointestinal in origin it seems to me that Dr. Holmes ought to see something in the gastrointestinal tract beyond a little pushing of the liver in a southeasterly direction. What can you tell about the gastrointestinal tract, Dr. Holmes? Is there anything else besides the pushing down of the liver?

DR. HOLMES: I did this examination myself and that is all I could or can see.

DR. MEANS: But you are willing to say that the liver is big.

DR. HOLMES: Yes.

DR. MEANS: There have been cases in which the radiologist has said that the liver was big and the clinician has said that it was not big, and Dr. Castleman has found that sometimes the radiologist was right and sometimes the clinician was right. But here both the clinician and the radiologist thought that the liver was big; ergo, I shall say that the liver was big. Of course if the patient had a chronic bronchopulmonary suppurative process with a big liver she is entitled to have had amyloid disease, but I do not think that amyloidosis would explain the acute picture of severe pain in the right upper quadrant.

I have said all I need to say about the lung situation. I do not believe that it was tuberculosis.

In these exercises we usually try to explain the whole picture on the basis of a single underlying disease. We are taught that that is the right thing to do in differential diagnosis. If you stick too rigidly to it, however, you come a "cropper" a certain number of times, because a person can have two diseases. Whether the five-day story of abdominal pain has anything to do with the thoracic story, I do not know. I suppose we should try to relate it, but it does not have to be related. One thing is evident. I am sure that she had an avitaminosis, which explains the stomatitis, the raw red tongue, the sensory changes, the reflex changes and so forth. The clinicians gave her high-powered vitamin therapy, so evidently they thought the same.

On physical examination we are told that this woman was well nourished, although she had lost weight. She might have been overweight to start with. I do not know why she did not look sick. She was said to be exhausted and was forced to stay in bed. Sometimes neurotics take to bed, but she was not neurotic I should say. I do not know



## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*\*

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

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#### CASE 31031

#### PRESENTATION OF CASE

A twenty-nine-year-old woman was admitted to the hospital complaining of a chronic productive cough and abdominal pain.

Twelve years prior to admission the patient began to suffer with chronic cough. This was often accompanied with fever and was productive at times of as much as a cupful of mucopurulent, foul-smelling sputum a day. The sputum was never blood streaked until a year before entry, when flecks of blood were first noted. The cough and streaking became increasingly severe and were associated with vomiting, often at the end of a paroxysm. On several occasions she vomited intractably for several days at a time. On two occasions she was said to have vomited blood, although at no time did the vomitus have a coffee-grounds appearance. About six months prior to entry a bronchoscopy and lipiodol study were performed, following which she felt better for a few weeks. The blood streaking of the sputum increased, however, until it occurred daily and was most marked in the morning. About three weeks prior to admission she became so exhausted that she was forced to remain in bed; the slightest exertion often induced a severe paroxysm of coughing followed by vomiting. She was able to retain little food, and the tongue and mouth became sore. She had lost about 16 pounds during the year before entry. Five days before admission she developed severe pain under the costal margin in the right upper quadrant, radiating to the epigastrium but not to the back. The pain occurred intermittently in attacks lasting up to twelve hours. There was no diarrhea, constipation, abnormal stools or jaundice. She was admitted to the hospital for study.

The patient had been married for three years but had been unable to become pregnant. She had been a heavy smoker but had cut down considerably in the few months prior to admission.

Physical examination revealed a well-developed and well-nourished woman who did not appear particularly ill. The tongue was beefy red and moderately smooth. The mouth contained numer-

ous small ulcers on the mucous membranes. The lungs revealed only a few medium moist rales at the bases. The heart was negative. There were considerable tenderness and muscle spasm in the right upper quadrant. A tender mass, believed to be the liver, was palpable in this area, extending down almost to the level of the umbilicus; no definite edge could be felt. The spleen was not palpable. There was a lack of precise differentiation between sharp and dull sensations in the lower legs, and some questionable loss of position sense. Vibration sense was diminished in the left lower leg. The deep tendon reflexes were present but the ankle jerks were weak. The plantar responses were not elicited.

The temperature was 99.4°F., the pulse 100, and the respirations 24. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood showed a white-cell count of 11,200, with 93 per cent neutrophils, 4 per cent monocytes and 3 per cent eosinophils. The hemoglobin was 11.8 gm. The urine had a specific gravity of 1.028, with a ++ test for albumin; the sediment contained a few red cells, 15 white cells and a rare granular cast per high-power field. The stools were brown, and a guaiac test was negative. The serum nonprotein nitrogen was 23 mg. per 100 cc., the sugar 78 mg., the protein 6.4 gm. and the chloride 94 milliequiv. per liter. The van den Bergh reaction was normal. The prothrombin time was 24 seconds (normal, 18 to 20 seconds). A bromsulphalein test showed 40 per cent retention of dye in forty-five minutes.

A roentgenogram of the chest was within normal limits. A gastrointestinal series revealed displacement of the stomach to the left and downward displacement of the hepatic flexure of the colon, but was otherwise negative. The lower border of the liver was not well demonstrated. An intravenous pyelogram revealed only a low right kidney. A Graham test was negative.

The patient was given numerous infusions of dextrose in saline together with vitamin B complex, haliver-oil capsules and hykinone. The white-cell count rose to 25,600, with 79 per cent neutrophils, 11 per cent lymphocytes, 8 per cent monocytes and 2 per cent eosinophils.

On the nineteenth hospital day a laparotomy was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. J. H. MEANS: "About six months prior to entry a bronchoscopy and lipiodol study were performed, following which she felt better for a few weeks." Are you holding back what was found?

DR. BENJAMIN CASTLEMAN: That is all that is in the record.

DR. CHESTER M. JONES: It was done elsewhere.

DR. MEANS: Apparently no Hinton test was done but I do not believe that the patient had syphilis.

acute surgical emergency. When I saw her she did not look so well as this record implies. She appeared extremely sick and was nauseated and vomiting; the white-cell count was 25,000, with 93 per cent neutrophils. She had definite spasm and tenderness in the right abdomen. I could not make a diagnosis, nor did I believe that she was sick enough to warrant immediate surgical operation.

DR. MEANS: Did you think that she had intestinal obstruction?

DR. MEIGS: No; I thought that she might have had a chronic rupture of some viscus. There was a mass on the right side. I could not feel the edge of the liver. All I knew was that we ought to get her some place where we could follow her closely. She was brought here. The next morning she looked better and the white-cell count had dropped. I thought that she had some disease connected with the liver. I asked Dr. Jones to see her. We thought that it was some sort of medical problem quite definitely connected with the liver. I did not believe that the pulmonary difficulties had anything to do with it. Dr. Richard H. Overholt had bronchoscoped her and found bronchiectasis. Dr. Jones carried on.

DR. JONES: By the time I saw the patient there was little in the chest except for a few rales, particularly at the right base. We all thought that she had a low-grade bronchiectasis to account for part of the clinical picture, but we did not believe that it had caused the symptoms that brought her to the hospital. She had a large mass, which Dr. Meigs and I both thought was probably a large liver. It was extremely tender for two weeks after admission to the hospital. We could not be certain whether the tenderness was along the hepatic border or underneath the edge of the liver. As she improved, with adequate hydration and rather intensive vitamin therapy for obvious avitaminosis, it became clear that the tender mass actually was liver. The one test that gave us a direct clue was the brom-sulfalein test, with 40 per cent dye retention in the absence of jaundice. Dr. Meigs and I decided that the sensible thing to do was to sit tight until she got better and then make absolutely certain that there was no disease besides the intrahepatic disease. For that reason she was explored.

The patient was explored with the idea that she had a subacute inflammatory, possibly cirrhotic, process in the liver, not necessarily on an infectious basis. We did not expect to find anything outside the liver. We simply wanted to make certain.

DR. MEANS: The chief point of disagreement between Dr. Jones, who saw the patient and therefore had more information, and me is whether the process in the liver was acute or subacute. There is nothing in the abstract on which I could say that it was other than acute. I did have cirrhosis down here on my list of differential diagnoses but forgot to mention it. You have to think of it because it is

a frequent liver disease producing a great variety of pictures and does produce pain and fever. There have been a number of such cases, I recall one in particular, that of a nurse who had acute pain and was rushed to the amphitheater and was operated on, only to find that she had a cirrhosis. Of course I shall have to agree that cirrhosis is a possibility.

#### CLINICAL DIAGNOSIS

Subacute hepatitis (? cirrhosis).

#### DR. MEANS'S DIAGNOSES

Acute infectious hepatitis (? multiple abscesses, ? cirrhosis).

Chronic bronchiectasis.

Avitaminosis (B complex).

#### ANATOMICAL DIAGNOSIS

Acute alcoholic hepatitis.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation a large fatty liver was found, and biopsy showed the findings that have been described in acute alcoholic hepatitis. It was not actually a cirrhosis, because at this stage there is no actual fibrosis. The liver cells were filled with fat, and many showed the hyaline network described years ago by Dr. Frank B. Mallory.\* This case showed it to an extreme degree, and around these areas there was a marked polymorphonuclear infiltration, which may have accounted for the elevated white-cell count. In the later stages of this condition there is a replacement of liver cells by connective tissue and a gradual decrease in the size of the liver to one perhaps a little larger than normal, but rarely smaller than normal.

DR. JONES: There was a real discrepancy in the history as regards the use of alcohol; I think that it is fair to say that the use of alcohol was not known to be excessive, but it may have been an important factor. Six months before entry — and this is not mentioned in the history — the patient had an episode that was clearly one of acute pellagra and that might have contributed to the development of liver disease when combined with alcohol and other unknown factors. The leukocytosis is not inconsistent with acute liver damage, even on a non-infectious basis — a point not generally recognized. I have seen a white-cell count as high as 35,000 with many immature cells, such as young myelocytes, in patients with rapidly progressing hepatic damage.

It is interesting to add that this patient has been extremely well since leaving the hospital and the liver has receded almost to the costal margin.

DR. MEANS: There was no definite history of alcoholism?

DR. MEIGS: No more than cocktail parties all last summer.

\*Mallory, F. B. *The Principles of Pathologic Histology*. Philadelphia: W. B. Saunders Company, 1914. Pp. 504-508.

whether she had syphilis. There is no reason to suppose that she did. I do not believe that she had tuberculosis of the liver, but she did have a big liver. I once met my Waterloo at a clinicopathological conference in St. Louis because I had a case of big liver and jaundice and asked Dr. Chester M. Jones before I got on the train if I should consider hepatic tuberculosis. He said, "No; it is so rare that you can forget it." But it was tuberculosis of the liver.

A word or two about the acute attack. I tried to think of the various possible causes. One should always think of lymphoma, but I do not believe that lymphoma could have explained the picture.

I should like to have more than one body temperature. Was it a septic chart?

DR. CASTLEMAN: No; it was flat, the temperature reaching 99.2°F. on only one occasion.

DR. MEANS: This is really difficult — an infectious process without any fever to speak of. I still do not believe that it was cancer. Cancer of what? Of the liver, I suppose. She could not have had cancer of the lung for twelve years, that is sure. Dr. Holmes could find nothing in the lung. If the acute attack was related to the process in the lung, it must have been a process in the lung that was infectious, such as a bronchiectasis. I looked up in some textbooks to see if there was any kind of suppurative process in the lung that gives rise to suppuration in the liver. I tried to find whether a suppurative bronchopulmonary disease may extend through the diaphragm and cause diaphragmatic abscess, thus dislocating the liver. We are told that it was a big displaced liver. I could not, however, find a word about that in my brief literary studies, so perhaps we cannot connect the two processes.

How about a blood-borne infection from the lung? Could a blood-borne infection get from the lung to the liver? It could through the hepatic artery, I suppose, but it seems extremely unlikely.

Let us see what we can get from the laboratory work? There were no lymphocytes in the first smear. I asked Dr. Wyman Richardson what that meant and he said that it made no sense to him; he added that it probably was a poor smear and that the examiner had counted only 100 cells. He is probably right, so that I am not going any farther with that. He also said that scarcity of lymphocytes was in favor of infection, but 3 per cent of eosinophils was against it. So there we are. They found some lymphocytes the next time though. The white-cell count was 25,000. This favors an infectious process. The nonprotein nitrogen, sugar and protein levels and the van den Bergh reaction were normal. The chloride was slightly down. The prothrombin time was only slightly elevated, but there was a positive bromsulfalein test. Would you call it an impressive dye retention, Dr. Jones?

DR. JONES: Forty per cent — yes.

DR. MEANS: So I am forced to believe that the liver was sick at least. She had a big sick liver.

What kind? Infectious, I think. How much hepatitis can one have without jaundice?

DR. JONES: A great deal.

DR. MEANS: She could have had acute cholecystitis, I suppose. That would fit this five-day story of severe pain at the right costal margin, radiating to the epigastrium but not to the back. It does not have to go into the back. One can have gall-bladder pain intermittently for twelve hours. That part of the story is all right, but with a big sick liver we must infer more than gall-bladder disease. Also, the Graham test was negative.

I thought of multiple liver abscesses in some way due to the old infection. I could not find any literary support for that hypothesis or for subdiaphragmatic abscess; but certainly there must have been something acute going on in the region of the liver, because of the acute onset of pain, the mounting white-cell count and the tenderness and spasm over the liver. I am much impressed by the last point.

That is the best that I can do. I mentioned a number of possibilities, some of which I am sure were not present. I believe that she had a chronic bronchiectasis. I believe that all the vomiting in the absence of any positive findings in the gastrointestinal tract ought to be interpreted as the result of terrific coughing. At any rate there is no positive evidence of gastrointestinal disease that permits a diagnosis, so that I shall stick to the facts and say that she had a chronic bronchopulmonary process, probably bronchiectasis of long standing. Did she have clubbed fingers?

DR. CASTLEMAN: No.

DR. MEANS: I do not believe that she had cancer, tuberculosis, actinomycosis or lymphoma. I mentioned the possibility of an amyloid liver, but that does not explain the full picture. I am therefore forced to say that she had some kind of infectious process of the liver. Where it came from I do not know. It may have been multiple abscesses. I do not believe that it could have been an amebic abscess.

DR. HOLMES: Were the sinuses examined? It is possible that the pus was coming from the sinuses instead of the lung.

DR. MEANS: A patient does not cough up a cupful of foul sputum daily and have symptoms for twelve years from a sinus.

DR. HELEN PITTMAN: Sinuses feed the bronchi.

DR. MEANS: Yes; but there has to be something in the bronchus.

DR. PITTMAN: I think that another point that Dr. Holmes brought out, namely, whether anyone saw the sputum, is a good one.

DR. MEANS: Well, of course, the whole history may be false, but I have to accept the facts given.

DR. CASTLEMAN: Dr. Meigs, will you tell us about your impression?

DR. J. V. MEIGS: This woman's acute illness necessitated a night visit. It was thought to be an

## CASE 31032

## PRESENTATION OF CASE

A thirty-three-year-old married woman was admitted to the hospital with malaise and diffuse distress in the lower abdomen.

One week prior to admission the patient's expected menstrual period did not appear. Instead she noted only slight staining, accompanied by a feeling of general malaise and weakness. Two days later she passed a small amount of blood per vaginam. She also noted slight soreness in the lower abdomen; this had no definite localization but gradually became more pronounced. One day prior to entry she again passed a small amount of blood. Although she felt rather "warm," there were no chills or fever. Her appetite was poor. There was no nausea, vomiting or diarrhea. She had had a normal bowel movement on the morning of admission.

The patient had been pregnant nine times and had had seven children. The last miscarriage had occurred six years before admission. Her menstrual periods were apparently regular. Physical examination revealed a well-developed and well-nourished woman. The heart and lungs were negative. The abdomen revealed generalized tenderness with slight spasm, most marked in the right lower quadrant. Peristalsis was normal. Pelvic examination revealed a slightly enlarged uterus in anterior position; it was very tender, especially on the right. The cervix was large and lacerated, with numerous nabothian cysts. A round, firm, exquisitely tender, golf-ball-sized mass was felt posteriorly.

The temperature was 99°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic. Examination of the blood showed a white-cell count of 11,000. The urine was negative. A laparotomy was immediately performed.

## DIFFERENTIAL DIAGNOSIS

Dr. John L. Newell: This woman of child-bearing age had missed one period, and in starting to discuss the case we must first try to determine whether she was pregnant. She had amenorrhea but no history of nausea. The uterus was slightly enlarged. No mention is made of any softening of the cervix. It was too early to get a definite Hegar's sign, but there should be softening, unless it was masked by scarring subsequent to lacerations at previous childbirths. I think it is fair to assume, however, that she had an early pregnancy and that, with this irregular spotting, there was a threatened abortion. Whether the pregnancy was intrauterine or extrauterine is the next question to decide. The uterus is described as being enlarged and tender. The tenderness puzzles me somewhat because, unless

The next thing that comes to mind is the firm, — and I emphasize the word "firm," — exquisitely tender mass, about 4 cm. in diameter, in the pouch of Douglas. If she had an extrauterine pregnancy and had had an incomplete tubal abortion, having pushed the ovum into the peritoneal cavity, the mass should not be that large, and at this stage of pregnancy it should not be so firm as described. I shall return to that later.

The abdominal findings are interesting. She had a history of pain, which became severer over a period of days. She had also tenderness, chiefly localized in the right lower quadrant. This, of course, is consistent with an incomplete tubal abortion, and that is also true for the temperature, pulse, blood pressure and leukocytosis. The main point in my mind against an ectopic pregnancy is this mass. I believe that she had a twisted cyst of the right ovary. Whether the cause of the abortion was the fact that the corpus luteum happened to be in the right ovary, I do not know; that would be a perfectly logical conclusion.

Dr. Fred A. Simons, Jr.: According to our experience in the Emergency Ward, the presence of a mass in the pelvis that is exquisitely tender is this patient did have a tubal pregnancy. Dr. Edward Hamlin, Jr.: Would it not be unusual for the mass to be described as round, firm and golf-ball-sized? The description alone, if it is accurate, argues against tubal pregnancy; such a mass is usually indefinite with the amount of pressure that one can use and is seldom firm. Dr. Newell: This ovum was only three weeks of age. If it had been aborted into the pouch of Douglas, the mass might be as large as a golf ball because of surrounding blood clot, but it should not be firm and hard.

Dr. Francis M. Ingersoll: I agree that it seems much more like a cyst that had twisted than a tubal pregnancy; she may have had an intrauterine pregnancy that was ready to abort.

## CLINICAL DIAGNOSIS

Tubal pregnancy.

Dr. Newell's Diagnoses

Cyst of right ovary, with torsion.  
Probable intrauterine pregnancy.

## CASE 31032

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The patient had been pregnant nine times and had had seven children. The last miscarriage had occurred six years before admission. Her menstrual periods were apparently regular.

Physical examination revealed a well-developed and well-nourished woman. The heart and lungs were negative. The abdomen revealed generalized tenderness with slight spasm, most marked in the right lower quadrant. Peristalsis was normal. Pelvic examination revealed a slightly enlarged uterus in anterior position; it was very tender, especially on the right. The cervix was large and lacerated, with numerous nabothian cysts. A round, firm, exquisitely tender, golf-ball-sized mass was felt posteriorly.

The temperature was 99°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood showed a white-cell count of 11,000. The urine was negative.

A laparotomy was immediately performed.

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there had been an attempt at a criminal abortion, I cannot interpret it. What is meant I believe is that manipulation of the uterus, rather than manual pressure on the uterus itself, caused pain.

DR. BENJAMIN CASTLEMAN: The note says that the uterus was "very tender."

DR. NEWELL: I do not remember seeing either an intrauterine or an extrauterine abortion in which the uterus itself was tender. Tenderness in the right vault is to be expected if it was an extrauterine pregnancy.

The next thing that comes to mind is the firm, — and I emphasize the word "firm," — exquisitely tender mass, about 4 cm. in diameter, in the pouch of Douglas. If she had an extrauterine pregnancy and had had an incomplete tubal abortion, having pushed the ovum into the peritoneal cavity, the mass should not be that large, and at this stage of pregnancy it should not be so firm as described. I shall return to that later.

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Tubal pregnancy.

DR. NEWELL'S DIAGNOSES

Cyst of right ovary, with torsion.  
Probable intrauterine pregnancy.

## ANATOMICAL DIAGNOSIS

Acute salpingo-oöphoritis.

## PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: I am sorry that the surgeon who operated on this patient is not here. At operation he found a slightly enlarged uterus; the right tube was thick, red and reflected on itself, so that the fimbriated end lay in the posterior cul-de-sac and was held there by adhesions. The left tube was also slightly reddened but normal in size and shape. The right ovary was moderately enlarged, firm and intimately connected with the enlarged right tube. The tube and ovary were removed.

The preoperative and postoperative diagnoses were ectopic pregnancy, but microscopic examination showed no evidence of pregnancy. The tube was markedly edematous and filled with pus. It was one of the most acutely inflamed tubes that we have seen for a long time, but of course they are usually not removed in the acute stage. There was

acute inflammatory disease of the pelvis, which had involved the right tube and ovary and, to a lesser degree, the left tube. There was probably also an acute endometritis, which perhaps accounted for the slight increase in the size of the uterus.

DR. SIMMONS: Was she pregnant?

DR. CASTLEMAN: No; a Friedman test done after operation was negative, which ruled out an intra-uterine pregnancy. I do not believe that pregnancy could have occurred in the presence of such a pyosalpinx.

DR. SIMMONS: Is it not true that you frequently receive specimens from patients who clinically have proved tubal pregnancies in which you do not find decidua or villi?

DR. CASTLEMAN: In such cases the tubes are filled with blood and there is no acute infection in the wall of the tube. In this case there was inflammation in the wall of the tube, frank pus within it, and fibrin on its surface. There is no doubt about the diagnosis.

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DR. JOHN L. NEWELL: This woman of child-bearing age had missed one period, and in starting to discuss the case we must first try to determine whether she was pregnant. She had amenorrhea but no history of nausea. The uterus was slightly enlarged. No mention is made of any softening of the cervix. It was too early to get a definite Hegar's sign, but there should be softening, unless it was masked by scarring subsequent to lacerations at previous childbirths. I think it is fair to assume, however, that she had an early pregnancy and that, with this irregular spotting, there was a threatened abortion. Whether the pregnancy was intrauterine or extrauterine is the next question to decide. The uterus is described as being enlarged and tender. The tenderness puzzles me somewhat because, unless

there had been an attempt at a criminal abortion, I cannot interpret it. What is meant I believe is that manipulation of the uterus, rather than bimanual pressure on the uterus itself, caused pain.

DR. BENJAMIN CASTLEMAN: The note says that the uterus was "very tender."

DR. NEWELL: I do not remember seeing either an intrauterine or an extrauterine abortion in which the uterus itself was tender. Tenderness in the right vault is to be expected if it was an extrauterine pregnancy.

The next thing that comes to mind is the firm, — and I emphasize the word "firm," — exquisitely tender mass, about 4 cm. in diameter, in the pouch of Douglas. If she had an extrauterine pregnancy and had had an incomplete tubal abortion, having pushed the ovum into the peritoneal cavity, the mass should not be that large, and at this stage of pregnancy it should not be so firm as described. I shall return to that later.

The abdominal findings are interesting. She had a history of pain, which became severer over a period of days. She had also tenderness, chiefly localized in the right lower quadrant. This, of course, is consistent with an incomplete tubal abortion, and that is also true for the temperature, pulse, blood pressure and leukocytosis. The main point in my mind against an ectopic pregnancy is this mass. I believe that she had a twisted cyst of the right ovary. Whether the cause of the abortion was the fact that the corpus luteum happened to be in the right ovary, I do not know; that would be a perfectly logical conclusion.

DR. FRED A. SIMMONS, JR.: According to our experience in the Emergency Ward, the presence of a mass in the pelvis that is exquisitely tender is definite evidence of tubal pregnancy. I believe that this patient did have a tubal pregnancy.

DR. EDWARD HAMLIN, JR.: Would it not be unusual for the mass to be described as round, firm and golf-ball-sized? The description alone, if it is accurate, argues against tubal pregnancy; such a mass is usually indefinite with the amount of pressure that one can use and is seldom firm.

DR. NEWELL: This ovum was only three weeks of age. If it had been aborted into the pouch of Douglas, the mass might be as large as a golf ball because of surrounding blood clot, but it should not be firm and hard.

DR. FRANCIS M. INGERSOLL: I agree that it seems much more like a cyst that had twisted than a tubal pregnancy; she may have had an intrauterine pregnancy that was ready to abort.

## CLINICAL DIAGNOSIS

Tubal pregnancy.

## DR. NEWELL'S DIAGNOSES

Cyst of right ovary, with torsion.

Probable intrauterine pregnancy.

V. D.

THE war against V. D. is going well. Turner<sup>1</sup> in reporting on the control of these diseases since 1940 points out that the yearly time lost from these infections in the United States Army has been reduced from 1278 days per 1000 men in 1940 to 368 days in 1943. The Army data also show that the V. D. morbidity rate is below the preceding peace level and half that of World War I.<sup>2</sup> In civilian life a review of the figures for all states for 1943-1944 shows 100,000 fewer cases of syphilis than previously; in only thirteen states were there more cases than before, and in most of these states the increase was slight.<sup>3</sup>

Much credit for these excellent results among military personnel must be given to the appointment of V. D. C. (venereal-disease-control) officers in the Army and in the United States Public Health Service. Their conscientious efforts at various stations deserve every commendation that can be bestowed. Much has been attained by applying the principles of preventive medicine to these diseases. Such a program has been well outlined in a recent number of *Lancet* by Gordon.<sup>4</sup> It is to be hoped that this program can be carried over into civilian life in the postwar period.

These V. D. C. officers have also had the advantage of the apparently improved therapeutic measures that have been developed in the last four or five years. The progress report in this issue of the *Journal* reviews these new methods of treatment—the use of penicillin and the sulfonamides, the intensive use of arsenicals and their combination with fever therapy and so forth. This report also strongly emphasizes the need for caution in universally adopting these procedures until they have been found to be safe and have been proved to produce, in the long run, as good or better end results than the present-day accepted methods of treatment have accomplished.

Many other matters in connection with these diseases need further thought and discussion. The matter of juvenile delinquency has been found to be tied closely to this problem, and every agency should be mobilized to aid in the solution of reaching the family and the small community. Educa-

tion of the civilian population in matters pertaining to these diseases has been stressed and much has been done, but further effort is needed. Demobilization will bring its problems. Will the venereally infected veteran be discharged before cure to carry the infection back to civilians, or will he be held and paid as a soldier until cured? Will the experience of the V. D. C. officers in this field be put to use in civilian life to lessen further the incidence of these diseases? Time only can answer these and other questions.

With the epidemiologic principles set forth by Gordon and the experience gained in the war, with adequate regulations and their enforcement regarding contagious disease and with the rational use of the new therapeutic procedures, the demobilized V. D. C. officer can contribute greatly to a further decrease in the incidence of venereal disease.

REFERENCES

1. Turner, T. B. Immediate wartime outlook and indicated postwar conditions with respect to control of venereal diseases. *Am. J. Pub. Health* 33:1309-1315, 1943.
2. Turner, T. B., and Sternberg, T. H. Management of venereal diseases in army. *J. A. M. A.* 124:133-137, 1944.
3. Health officers' monthly statement: reported for fiscal years 1943-44 and 1942-43. *Fen. Dir. Inform.* 25:320, 1944.
4. Gordon, J. E. Control of venereal diseases: epidemiological approach. *Lancet* 247:711-715, 1944.

MASSACHUSETTS MEDICAL SOCIETY  
STATED MEETING OF THE COUNCIL

A stated meeting of the Council of the Massachusetts Medical Society will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, February 7, 1945, at 10:30 a.m.

Business:

1. Call to order at 10:30 a.m.
2. Presentation of record of meeting held October 4, 1944, as published in *The New England Journal of Medicine*, issue of December 21, 1944.
3. Reports of standing and special committees.
4. Appointment of delegates:
  - (a) To the House of Delegates, American Medical Association, for two years from June 1, 1945.
  - (b) To the annual meetings of the five New England state medical societies in 1945.
  - (c) To the Annual Congress of the American Medical Association on Medical Education and Licensure at the Palmer House, Chicago, February 12 and 13, 1945.
5. Such other business as may lawfully come before this meeting.

MICHAEL A. TIGHE, M.D., *Secretary*

DEATHS

MAHONEY—John L. Mahoney, M.D., formerly of Boston, died January 2 at St. Petersburg, Florida. He was in his seventy-third year.  
Dr. Mahoney received his degree from Boston University School of Medicine in 1898.



**WIGGIN** — William I. Wiggin, M.D., of Lowell, died January 3. He was in his sixty-sixth year.

Dr. Wiggin received his degree from McGill University Medical School in 1901. During World War I he served overseas for eighteen months with a Red Cross field unit. He taught otolaryngology at Harvard Medical School from 1919 until his retirement a few years ago. During the same period he served as staff surgeon at the Massachusetts Eye and Ear Infirmary. He had also been a member of the Lowell General Hospital staff for many years. He was a fellow of the American College of Surgeons and the American Medical Association, and a member of the American Board of Otolaryngology, the American Academy of Ophthalmology and Otolaryngology, and the New England Otological and Laryngological Society. At the time of his death, he was vice-president of the Middlesex North District Medical Society.

His widow and his mother survive.

## CORRESPONDENCE

### TREATMENT OF THE COMMON COLD

*To the Editor:* In the April, 1944, issue of the *Journal of the Maine Medical Association* there appeared an article by me which was a review of outstanding work pertaining to the common cold. The review was made because of the fact that a number of patients had divulged that they had received "cold serums" and other useless forms of medication that, on the whole, seemed to be perhaps more harmful than good.

The onset of the common cold — the virus stage — is characterized by sneezing, watery discharge and stuffiness of the nose, with a subnormal or normal temperature. Influenza, on the other hand, has a sudden onset with fever, headache and neuromuscular or gastrointestinal manifestations.

During the virus stage of the common cold, which lasts for three or four days, immediate and proper treatment can abort the secondary phase of this ailment.

One must avoid drying, mentholated, creamy or oily nose medication, cathartics and alcohol. Equally useless, in my mind, are the vitamins (in the otherwise healthy person), sulfonamides, soda, aspirin, calcium and iodine, liver oil, amyral, ephedrine, atropine, quinine and like drugs.

The crux of the treatment for the virus phase of the common cold is in the intelligent use of the hot bath and medication with the opium derivatives, codeine and papaverine. Such treatment has never failed to abort the first stage of the common cold in any of my patients who followed directions explicitly.

Copavin, which is a commercial preparation containing  $\frac{3}{4}$  gr. each of codeine and papaverine, is given, the dosage being one tablet (or capsule) after meals and two at bedtime or one tablet every three hours and two at bedtime. The dosage is regulated according to the severity of the symptoms and to the size of the patient. If the symptoms are severe, two tablets may be given for the first and second doses and three at bedtime. For children the dosage is, of course, regulated according to size. The codeine-papaverine combination was conceived by Diehl and his co-workers, who observed that chronic users of opium and its derivatives were remarkably free from the common cold.

The hot-bath regime must be explained to the patient. The tub should be half full of hot water, and the body should be kept well immersed until perspiration occurs on the head (debilitated patients should not, of course, be submitted to this). From the bath the patient goes immediately to a warmed bed and remains there two or three hours in a well-aired room.

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LYOYD H. BERRIE, M.D.

Caribou, Maine

## BOOK REVIEWS

*The Romance of Medicine: The story of the evolution of medicine from occult practices and primitive times.* By Benjamin L. Gordon, M.D. 8° cloth, 624 pp., with 145 illustrations. Philadelphia: F. A. Davis Company, 1944. \$5.00.

This volume is not a history of medicine in the conventional biographic pattern; rather, it is a series of philosophic essays on the evolution of medicine from the standpoint of a number of its principal problems in primitive time — animism, reproduction, heredity, physiology, disease, demonology, witchcraft, hysteria, the evil eye, astrology, symbolism, superstition, scapegoatism, signature, biologic products, hydrotherapy, psychotherapy, medical ethics and immortality. Under each of these subjects the author surveys the field from prehistoric to modern time, with a wealth of scholarly allusion, quotation and reference. Everything in modern medicine has derived, often in devious ways, from the earliest past. That is what to him constitutes its romance.

The book contains excellent illustrations, many of which are unfamiliar. The footnotes, which afford a compendium of strange information and references in addition to those of the text, are extremely valuable.

The more one contemplates the eccentricities of the past, the less one wonders at those of the present. No book is quite like this, unless it be Dr. Howard W. Haggard's *Devils, Drugs and Doctors* of fifteen years ago. Dr. Gordon's essays are wider-ranging, but all are from the same point of view. It is unfortunate that so excellent a work is marred by so many obvious misprints; the book is, nevertheless, a worthy achievement of scholarship.

*The Dental Treatment of Maxillo-Facial Injuries: With supplementary material on cases and techniques.* By W. Kelsey Fry, M.C., M.R.C.S., L.R.C.P., L.D.S., R.C.S. (Eng.), P. Rae Shepherd, L.D.S., R.C.S. (Eng.), Alan C. McLeod, D.D.S. (Penn.), B.Sc. (dent., Toronto), L.D.S., R.C.S. (Eng.), and Gilbert J. Parfitt, M.R.C.S., L.R.C.P., L.D.S., R.C.S. (Eng.). With foreword by Professor F. R. Fraser, M.D., F.R.C.P., and a section on fractures of the middle third of the face by A. H. McIndoe, M.S., F.R.C.S., F.A.C.S. 8°, cloth, 434 pp., illustrated. Philadelphia: J. B. Lippincott Company, 1944. \$6.50.

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Caribou, Maine

Lloyd H. Barker, M.D.

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*Technique in Trauma: Planned timing in the treatment of wounds including burns.* From the Montreal General Hospital and McGill University. By Fraser B. Gurd, M.D., C.M.; and F. Douglas Ackman, M.D., C.M. In collaboration with John W. Gerrie, M.D., C.M., Edward S. Mills, M.D., C.M., Joseph E. Pritchard, M.D., and Frederick Smith, M.D. Preface by John S. Lockwood, M.D. With commentary by Ralph R. Fitzgerald, M.D., C.M. 4<sup>o</sup>, cloth, 68 pp., with 3 plates, 17 figures, 5 tables and 3 charts. Philadelphia: J. B. Lippincott Company, 1944. \$2.00.

This book consists of three papers published within the last two years, together with an introduction and a commentary that represent new material. These papers outline the detailed directions now being used in the Montreal General Hospital, treatment being based on the use of the most advanced and modern concepts that are now current in the surgical world. They therefore make available to the practitioner and student, in easily assimilable form, methods of treatment that have been safely and successfully used. Anyone who is occasionally or frequently confronted with decisions in the care of serious burns, extensive soft-part injuries or compound fractures can well afford to buy and give careful thought to the contents of this book.

Above all, it stresses that no individual can give adequate treatment to these cases but that carefully trained teams are necessary. This has been a universal experience in the last few years, but the organization of the necessary teamwork has seldom been discussed.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Infants without Families: The case for and against residential nurseries.* By Anna Freud; and Dorothy Burlingham. 12<sup>o</sup>, cloth, 128 pp. New York: International University Press, 1944. \$2.00.

This monograph deals with the care of homeless and parentless children, made so by the exigencies of war. It is based on the authors' experience at the Hempstead Nurseries in England. An attempt has been made to evaluate the advantages and disadvantages of institutional life at different phases of the infant's development. The text is divided into a number of chapters having to do with the aspects of development between birth and two years, early relations between institutional infants, introduction of the mother-relation into the nursery life, some aspects of instinctual satisfaction and frustration in family and nursery life, the role of the father in the residential nursery and the growth of the child's personality under nursery conditions. The authors conclude that institutional nurseries offer excellent opportunities for detailed and unbroken observation of child development but agree that the continuance of such nurseries after the war will be decided probably by social and economic needs and not on the basis of psychological requirements. The primary objective of the book is to discuss the questions: Should residential nurseries be maintained and, if so, can they be changed so as not to produce the so-called "institutional child"?

*Man Does Not Stand Alone.* By A. Cressy Morrison. 12<sup>o</sup>, cloth, 107 pp. New York: Fleming H. Revell Company, 1944. \$1.25.

This small book attempts a review of the scientific evidence of the existence of a supreme intelligence and is written as a challenge to Julian Huxley's *Man Stands Alone*, in which Mr. Huxley states that he does not believe in God or gods.

*Bailey's Textbook of Histology.* Revised by Philip E. Smith, Ph.D., professor of anatomy, College of Physicians and Surgeons, Columbia University; and Wilfred M. Copenhaver, Ph.D., associate professor of anatomy, College of Physicians and Surgeons, Columbia University. With the assistance of

Aura E. Severinghaus, Ph.D., associate professor of anatomy, College of Physicians and Surgeons, Columbia University; and Charles M. Goss, M.D., professor of anatomy, University of Alabama Medical School. Eleventh edition. 8<sup>o</sup>, cloth, 786 pp., with 470 illustrations. Baltimore: The Williams and Wilkins Company, 1944. \$6.00.

This edition of an authoritative teaching text, first published in 1904, has been thoroughly revised. The primary objective of providing a text for first-year medical students has been adhered to as in previous editions. The chapter on the female reproductive system has been amplified by the addition of a section on the placenta. The text throughout the book has been brought up to date and in places has been extended or clarified. Many new figures in color and halftone have been introduced throughout the book. Lists of carefully selected bibliographic references are appended to each chapter.

*Heart Disease.* By Paul D. White, M.D., lecturer in medicine, Harvard Medical School, and physician, Massachusetts General Hospital, Boston. Third edition, completely revised and reset. 8<sup>o</sup>, cloth, 1025 pp., with 138 illustrations. New York: The Macmillan Company, 1944. \$9.00.

This standard treatise has been thoroughly revised and brought up to date. An important addition is a chapter on the range of the normal heart. New material added includes phonocardiography, precordial leads, ligation of the patent ductus arteriosus, treatment of subacute bacterial endocarditis, splanchnic resection for hypertension, intracardiac thrombosis, pulmonary embolism and the heart in gastrointestinal diseases. There is also a new section on heart disease in military service. Many of the historical references that appeared in the first edition and were omitted in the second have now been replaced, owing to a demand from the readers of the book. New references to articles of importance appearing during 1937-1943 have been added after each chapter, whereas many of the references of current interest in the years 1931-1936 have been omitted. In order to obtain a complete bibliography one must consult the editions of 1931 and 1937. A number of illustrations have been added to the text.

*Fundamentals of Internal Medicine.* By Wallace M. Yater, M.D., M.S. (med.), professor of medicine and director of the Department of Medicine, Georgetown University School of Medicine, physician-in-chief, Georgetown University Hospital, and physician-in-chief, Gallinger Municipal Hospital, Washington, D. C. Second edition. 8<sup>o</sup>, cloth, 1204 pp., with 275 illustrations. New York: D. Appleton-Century Company, Incorporated, 1944. \$10.00.

The second edition of this book has been revised to conform to war conditions. New material of interest to the military internist has been added, including medical problems incidental to flying, immersion foot, blast injuries, effects of chemical warfare, war neuroses and tropical medicine. Many other subjects have been added or revised, including blood-typing, liver-function tests and a preliminary evaluation of penicillin. Three new sections have been written entitled "Symptomatic and Supportive Treatment," "Clinical Values and Useful Tables" and "The Physician Himself." A more comprehensive index has been made, and additional illustrations have been inserted in the text. The objective of this book is to include in one volume all the clinical subjects that an internist may encounter in his daily work.

*The Electrocardiogram: Its interpretation and clinical application.* By Louis H. Sigler, M.D., attending cardiologist and chief of the Cardiac Clinic, Coney Island and Harbor hospitals, New York. 8<sup>o</sup>, cloth, 403 pp., with 203 illustrations. New York: Grune and Stratton, Incorporated, 1944. \$7.50.

The objective of this book is to present in a simple but comprehensive manner all that relates to the electrocardiogram and its practical application to cardiology. The work is well illustrated with figures comprising nearly four hundred electrocardiograms. The book is divided into twenty-five chapters beginning with the biological and physical foundations of the electrocardiograph, its recording and the classification of electrocardiograms, followed by chapters on the various cardiac disorders.

*Rehabilitation, Re-education and Remedial Exercises.* By Olive F. Guthrie Smith, M.B.E., C.S.M.M.G., T.M.G., principal of the Swedish Institute, London, and director of

the Physical Exercise Department, St. Mary's Hospital. With a foreword by Lord Horder, G.C.V.O., M.D., F.R.C.P. 8°, cloth, 424 pp., with 273 illustrations. Baltimore: The Williams and Wilkins Company, 1943. \$6.00.

This book is devoted primarily to a discussion of remedial exercises in various orthopedic conditions, with emphasis on the suspension methods of the author.

*X-Ray Examination of the Stomach: A description of the roentgenologic anatomy, physiology and pathology of the esophagus, stomach and duodenum.* By Frederic E. Templeton, M.D., head of the Department of Roentgenology, The Cleveland Clinic. 8°, cloth, 516 pp., with 297 illustrations. Chicago: The University of Chicago Press, 1944. \$10.00.

This monograph is devoted to an intensive study of the upper digestive tract by the x-ray. It includes a presentation of modern, roentgenologic methods and their use and interpretation, together with the detailed consideration of the normal and abnormal manifestations encountered in the stomach, esophagus and duodenum, with careful, differential diagnosis. The filming fluoroscope is described and discussed. The work is well illustrated and printed on heavy paper in a legible type.

*Insulin Shock Therapy.* 8°, paper, 97 pp., with 13 tables. New York: Temporary Commission on State Hospital Problems, 1944. Available, without cost, on application.

The commission recommends that insulin-shock therapy for dementia praecox be made available in all the state hospitals for the insane in New York. The recommendation is based on the results of an intensive study of 1128 dementia-praecox patients treated with insulin shock at the Brooklyn State Hospital in five and a half years and a comparable group of 876 patients admitted to the state hospitals in the metropolitan area who did not receive that form of treatment. The commission found that insulin-treated patients did better in all respects than a group not so treated. More patients left the hospital after a shorter stay, and a larger number were living usefully at home. It was also found that over half the institutional population of mental hospitals was made up of dementia-praecox cases. The reports showed great direct savings in hospital days and in the cost of food and clothing and undetermined indirect savings in maintenance costs and ultimately in construction costs. The commission was appointed in November, 1940, and made a progress report in November, 1942, at which time it recommended the extension of shock therapy, as well as increasing the number of patients placed on parole or in family care. It stated that increased effort in these directions had not only halted the rate of increase of patients in state hospitals but that during a four-month period in 1942 the long-standing average increase of about 2400 patients had given place to a decrease of 78. This was the first such reversal in fifty years of state care of the insane. The commission concludes that insulin-shock therapy produces substantially better results in the treatment of dementia praecox than those obtained when insulin is not administered. What is more striking, good results were obtained even in those cases in which the prognosis without insulin is usually doubtful, such as patients in the older age groups, those whose illnesses have a duration of more than a year and those with a gradual onset.

*New and Nonofficial Remedies, 1944.* Issued under the direction and supervision of the Council on Pharmacy and Chemistry, American Medical Association. 12°, cloth, 778 pp. Chicago: American Medical Association, 1944. \$1.50.

The current volume of *New and Nonofficial Remedies* reflects two important and forward-looking decisions of the Council, namely, to use the metric system exclusively in all its publications and to consider for acceptance contraceptive preparations offered for use as prescribed by physicians.

The chapter on contraceptives is quite comprehensive, and the Council has thus far accepted certain contraceptive jellies and creams, diaphragms, diaphragm inserts, syringe applicators and fitting rings.

A number of new preparations are described. Certain general articles have been revised to bring them up to date, and more or less important revisions have been made in other chapters.

*Surgical Disorders of the Chest: Diagnosis and treatment.* By J. K. Donaldson, M.D., associate professor of surgery and in charge of thoracic surgery, University of Arkansas School of Medicine, and member of surgical staff, St. Vincent's Infirmary, and visiting staff, Baptist Hospital, Little Rock, Arkansas. 8°, cloth, 364 pp., with 127 illustrations. Philadelphia: Lea and Febiger, 1944. \$6.50.

This new work on thoracic surgery has been written primarily for general practitioners, general surgeons and students. It contains in a simple form the advances made in the field of chest surgery during the past decade. In line with this objective, controversial discussions, long statistical and historical reviews, unnecessary detail and long bibliographies have been omitted. Some discussion pertaining to war injuries has been included, although the author believes that the fundamental problems, with a few exceptions, are the same in both war and civilian injuries of the chest.

*The Art of Anaesthesia.* By Paluel J. Flagg, M.D., visiting anesthetist to Manhattan Eye and Ear Hospital, consulting anesthetist to St. Vincent's Hospital, New York, consulting anesthetist to the Woman's Hospital, Sea View Hospital, Jamaica Hospital, Mount Vernon Hospital, Flushing Hospital, Mary Immaculate Hospital, St. Mary's Hospital (Far Rockaway) and Nassau Hospital, Long Island. Seventh edition. 8°, cloth, 517 pp., with 166 illustrations. Philadelphia: J. B. Lippincott Company, 1944. \$6.00.

Five years have elapsed since the sixth edition of this standard text was published. During this period much progress has been made in the field of anesthesia. This edition discusses thoroughly the pros and cons of military anesthesia, as well as the newer developments in the field of anesthesia.

*The Gastro-Intestinal Tract: A handbook of roentgen diagnosis.* By Fred J. Hodges, M.D., professor of roentgenology, University of Michigan Medical School. 8°, cloth, 320 pp., with 130 plates. Chicago: The Year Book Publishers, Incorporated, 1944. \$5.50.

This manual consists of a large number of reproductions of x-ray films, with running descriptions of each.

*The Analysis and Interpretation of Symptoms.* Edited by Cyril M. MacBryde, M.D. 8°, cloth, 301 pp., illustrated. Philadelphia: J. B. Lippincott Company, 1944. \$9.00.

This symposium by ten specialists gives the basis for analysis and interpretation of some of the common symptoms found in patients. Emphasis is placed on the pathologic physiology of symptoms, whereas their correlation with other symptoms and with physical and laboratory evidence is considered as important but secondary in the diagnostic method.

## NOTICES

### NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held on Monday, January 29, at 8:15 p.m., at the Boston Medical Library.

#### PROGRAM

Echinococcal Heart Disease. Drs. Lewis Dexter and John Peters.

Some Clinical Effects of Cytochrome C in Anoxia. Drs. Samuel Proger, D. Decaneas and Gerhardt Schmidt.

Studies on Experimental Pulmonary Edema. Drs. A. A. Luisada and S. J. Sarnoff.

Insomnia Due to Unrecognized Left Ventricular Failure. Drs. Edwin Wheeler, Conger Williams, and Paul D. White.

Interested physicians and medical students are cordially invited to attend.

(Notices continued on page 22)

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## THE WATERHOUSE-FRIDERICHSEN SYNDROME\*

### Report of a Case With Recovery

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NEW YORK CITY

THE symptom complex known as the Waterhouse-Friderichsen syndrome was first described by Voelcker<sup>1</sup> in 1894. Early in 1944, Haas<sup>2</sup> found 144 cases reported in the literature, to which he added 3 of his own. Rucks and Hobson<sup>3</sup> stated that up to the beginning of 1942 there were 101 recorded cases, 26 of which had been reported in the preceding three years. Assuming that these workers did not overlook any cases up to the time of their respective communications, it appears that approximately 75 cases of the syndrome were reported between 1894 and 1939 and 75 in the five years from 1939 to 1943, inclusive. Since that time, Bernhard and Jordan<sup>4</sup> have reported 4 cases, Bush and Bailey<sup>5</sup> 6, and Meyer,<sup>6</sup> Martland<sup>7</sup> and Short and his associates<sup>8</sup> each 1, bringing the present total to 157. This suggests not so much an increased incidence as an increased interest in the disease and an improvement in methods for its recognition and treatment. Several excellent reviews and summaries have recently appeared,<sup>2-5,9,10</sup> but little has been said concerning the treatment, since the prognosis was hopeless prior to the advent of the sulfonamide drugs and potent adrenocortical preparations. Thus far, recovery has been reported in 11 patients.<sup>5,11-16</sup> Significant data, particularly in regard to treatment, from these cases and the one presented below are summarized in Table 1:

Of the 11 cases of Waterhouse-Friderichsen syndrome in which recovery has been reported, 3 were not described in sufficient detail to permit critical analysis,<sup>13,15</sup> but there seems to be little room for doubt about the diagnosis in any of them. Several features of special interest deserve to be emphasized.

#### Age Incidence

The Waterhouse-Friderichsen syndrome has been seen predominantly in children, Lindsay and his

co-workers<sup>17</sup> noting that 90 per cent of the patients were under nine years of age. On the other hand, of those who have recovered to date, only 1 was under the age of nine. In this case, the skin lesions were apparently much severer and the toxemia greater than in the other 10 patients. The recent increase in cases reported may be due to the high incidence in Army camps. Although the age incidence is of somewhat less importance from a statistical viewpoint since the number of cases is so small, mere coincidence hardly accounts for recovery in 11 adults and in only 1 child. Significance may also attach to the fact that the child ran the stormiest course of all and developed the severest skin manifestations, with large necrotic lesions. This is compatible with the general principle that children react in a more labile fashion than do adults and exhibit much profounder reactions to identical stimuli. The present patient, sixty-three years of age, is the oldest on record with recovery, and the only one in whom a preceding hypertension was known to have existed.

#### Etiology

In the earlier reports, a meningococcemia was postulated as the causative factor of the disturbance. At present, the etiology of the condition is far from settled. The meningococcus was cultured from the blood stream of 6 of the 12 patients who survived, *Staphylococcus aureus* from 1, and a pneumococcus from 1. One patient had a negative blood culture. In 3 cases there was no record of a study of the blood for organisms, but 2 of these showed organisms in the spinal fluid (Table 1).

The pathologic changes may be explained anatomically.<sup>3</sup> The frequency with which the meningococcus has been recovered from blood and spinal fluid has supported the concept of an organismal ectodermal tropism, in which the skin, adrenal glands and brain are simultaneously involved.<sup>18</sup> Cerebral changes have been demonstrated histologically.<sup>19</sup>

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## Morbidity

The rapidity with which reports have been appearing in the recent literature suggests that the Waterhouse-Friderichsen syndrome occurs much more frequently than was formerly thought. The average incidence in the last 485 cases of meningitis reported from Army camps <sup>4-6,20</sup> was 3.3 per cent; it occurred in 4 of 182 patients,<sup>4</sup> 5 of 134,<sup>20</sup> 6 of 126,<sup>5</sup> and 1 of 43.<sup>6</sup>

## Treatment

Sulfonamides were used in the treatment of each of the 12 cases (Table 1). Sulfanilamide was administered in 1, beginning forty-eight hours after onset. In this case, the quantities given were small

Watery extracts of the adrenal cortex were given in 10 cases. Desoxycorticosterone acetate alone was used in 2 patients,<sup>15</sup> and in conjunction with watery extracts in 3 cases,<sup>5,12</sup> as well as in the case reported below. The administration was unavoidably delayed for as long as thirty-six hours in 1 patient,<sup>3</sup> despite which the authors believe that it played an important role in maintaining the equilibrium between the tissues and the circulation, was definitely responsible for the stabilization of the blood pressure, and stimulated carbohydrate metabolism. It appears to have aided materially in terminating the stupor. The dosages of cortical hormone have not been large, in 1 case only 20 cc. of the watery extract being given during the second day after the

TABLE 1. Summary of Data in all Recovered Cases.

SOURCE	AGE	SEX	BLOOD CULTURE	BLOOD PRESSURE ON ADMISSION mm.Hg.	ADRENOCORTICAL THERAPY				SULFONAMIDE AND SPECIFIC THERAPY				OTHER THERAPY
					INTERVAL AFTER ONSET hr.	REPEAT INTERVAL hr.	INITIAL DOSE*	TOTAL DOSE*	PREPARATION	INTERVAL AFTER ONSET hr.	INITIAL DOSE	TOTAL DOSE	
Carey <sup>11</sup>	27	F	Meningococcus	63/35	16	4-5	10 cc.	50 cc.	Sulfanilamide Mgc. antiserum	48 24	5.5 gm. ?	50 gm. 170+cc.	Epinephrine (1:1000); 1 cc.
Grace, Harrison and Davie <sup>13</sup>	40	F	?	Low	?	?	?	?	A sulfonamide	?	?	?	
Bickel <sup>12</sup>	24	F	Pneumococcus	80/50	9 30	10-12 24	10 cc. 10 mg.	20 cc. 50 mg.	Sulfathiazole	9	2.0 gm.	37 gm.	Camphor in oil 2 cc.; epinephrine (1:1000), 1 cc.; Coramine, 2 cc.; Ephedrine, 1 cc.
Sharkey <sup>14</sup>	40	F	Sterile§	65/?	15	2	10 cc.	70 cc.	Sulfapyridine	15	3.0 gm.	36 gm.	
Rucks and Hobson <sup>3</sup>	3	M	Staph. aureus	Too low to obtain	36	4-6	5 cc.	90 cc.	Sulfathiazole	36	0.6 gm.	8 gm.	Epinephrine (1:1000), 0.2 cc.; vitamin K.
McCarty and Infield <sup>15</sup>	?	M	Meningococcus	Low	?	2	10 mg.	?	Sulfadiazine Mgc. antitoxin	?	4.0 gm. 50,000 units	?	
Peabody <sup>16</sup>	19	F	Meningococcus	60/40	?	?	20 cc.	40 cc.	Sulfadiazine	?	5.0 gm.	?	
Bush and Bailey <sup>5</sup>	?	M	Sterile	80/60	?	4	10 mg. 20 cc.	80 mg. 75 cc.	Sulfadiazine Mgc. antitoxin	?	5.0 gm. 20,000 units	?	
Meyer <sup>8</sup>	23	M	Meningococcus	70/45	?	?	?	?	Sulfadiazine Mgc. antiserum	0 ?	5.0 gm. ?	?	
Weinberg and McGavack	63	F	Meningococcus	100/50	3	3 3-12	10 mg. 10 cc.	20 mg. 70 cc.	Sulfadiazine	5	7.5 gm.	64.5 gm.	Coramine, 2 cc.; vitamins C and K.

\*Doses in cubic centimeters represent the watery extract, and those in milligrams, desoxycorticosterone acetate.

†Two cases of recovery mentioned but not described in detail.

‡Two cases of recovery mentioned but only one described in detail.

§Patient's serum subsequently gave a positive complement-fixation test with meningococci.

until the seventh day; antimeningococcus serum was injected shortly after onset and was continued with apparently good effect.<sup>11</sup> Sulfathiazole was used in 2 cases,<sup>3,12</sup> sulfapyridine in 1,<sup>14</sup> and sulfadiazine in the remaining 8. Although the azotemia and the abnormal urinary findings appear to contraindicate the use of sulfonamides, in no case has a renal complication been described. Moreover, the ready availability of these compounds and the severity of the condition under consideration amply justify their use either separately or in conjunction with antimeningococcus or other immune serums.

Antimeningococcus serum was employed for 3 patients, who appear to have responded no more rapidly than those in whom sulfonamides were used alone.

fulminant symptoms began.<sup>16</sup> Another patient was given 10 cc. nine and twenty hours respectively after the acute onset, followed by 10 mg. of desoxycorticosterone acetate at the thirtieth hour and daily thereafter for five days.<sup>17</sup> One case received 50 cc. of watery extract within the first twenty-four hours and none thereafter.<sup>11</sup> This had a striking beneficial effect on the blood pressure and mental status before either sulfonamides or antimeningococcus serums were employed. Sharkey<sup>14</sup> gave a total of 70 cc. of watery extract in four days, after which time his patient was out of danger. The largest doses of hormone were given by McCarty and Infield,<sup>15</sup> who used desoxycorticosterone acetate exclusively, administering 10 mg. every two hours until a systolic blood pressure of over 100 was obtained. Unfortunately, neither of their cases is



described in detail. Although desoxycorticosterone acetate is not a complete substitute for cortical deficiency, its ready availability and its profound effect on the blood pressure and the distribution of electrolytes warrant its routine use in all suspected cases of the Waterhouse-Friderichsen syndrome. In careful reading of the reports of the cases of patients who recovered, one gains the impression that a major portion of the early improvement in

Epinephrine was used with little recorded effect. Camphor and Coramine served as stimulants during the cyanotic phase of collapse in most of the patients, but their real value should be questioned.

### Laboratory Findings

Values for sodium and potassium were normal in 2 of the patients in whom determinations were

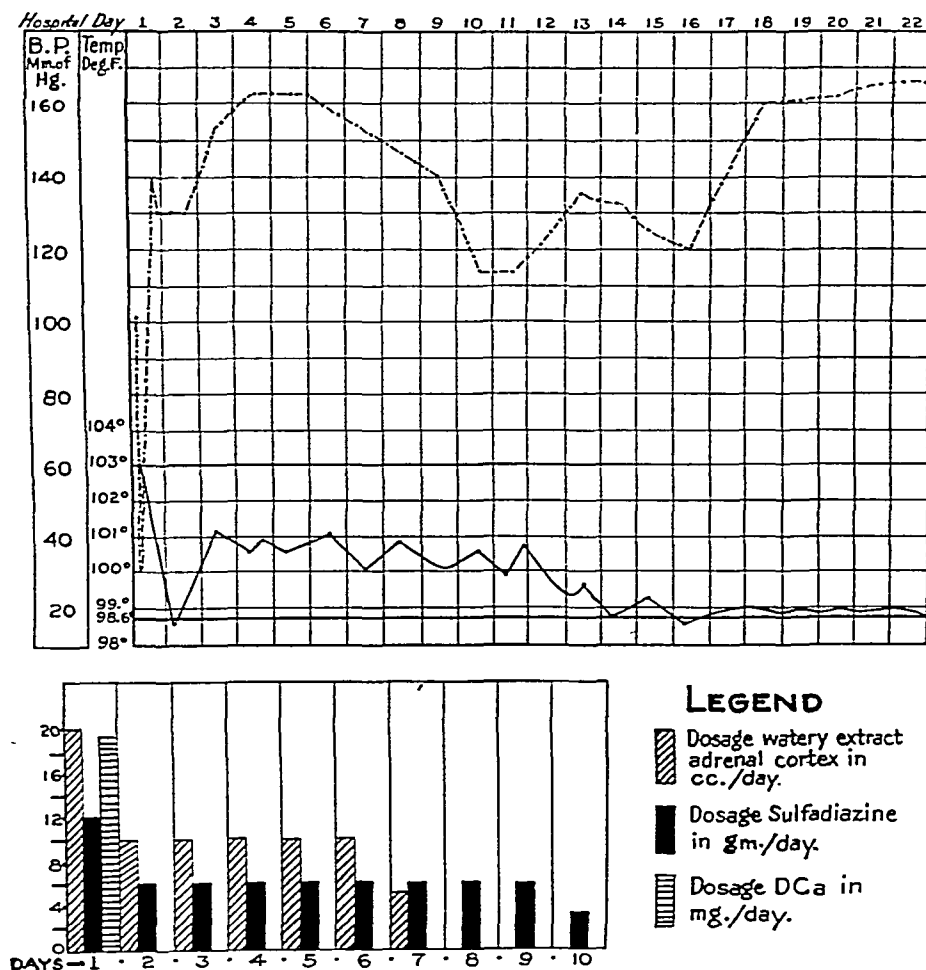


FIGURE 1.

mental status must be attributed to the hormonal therapy used.

The importance of cortical hormone in the treatment is still further emphasized by Haas's<sup>2</sup> description of his third case, which received adequate sulfonamide therapy but no hormone. The patient's condition grew steadily worse, with increasing stupor and death, nine hours after hospitalization and twenty hours after the onset of fulminant symptoms.

All the patients who recovered received liberal supportive treatment, chiefly in the form of intravenously administered glucose and saline solutions.

made,<sup>11,12</sup> as well as in our case, but a low sodium value was noted in Bush and Bailey's<sup>5</sup> patient; the chloride was extremely low (216 mg. per 100 cc.) initially in the case reported by Meyer,<sup>6</sup> to rise after recovery to 472 mg. Peabody's<sup>16</sup> patient had a normal chloride on admission. In such an acute condition, marked changes are more surprising than normal values since one would hardly expect to find variation in the electrolytes until there had been some depletion of readily available stores in interstitial fluid chambers. Even in patients with Addison's disease, Wilder and his associates<sup>21</sup> have demonstrated that the serum levels for these sub-



stances may be normal despite profound alterations in their behavior.

Histologic changes in the liver have been described in 2 cases of purpura fulminans in which the patients lived for eighty and eighty-eight hours, respectively.<sup>20</sup> In both patients, death was ascribed to hepatorenal failure. The case reported here is apparently the only one in which an attempt was made to appraise liver function during life.

### CASE REPORT

A 63-year-old woman was admitted to the hospital in a deep stupor within 1 hour after she had collapsed at work. She had had a sore throat 3 days prior to hospitalization and a mild headache the evening before. It was subsequently revealed that she had had mild exertional dyspnea and hypertension for 5 years and an equivocal history for 20 years of pernicious anemia, which had been controlled by occasional

urinary abnormality. A blood Wassermann reaction was negative, but a Kahn reaction was +. The white-cell count was 30,200, with 90 per cent neutrophils, of which 30 per cent were immature. The red-cell count was 3,700,000, with 78 per cent hemoglobin and a color index of 1.05. No organisms were found in direct smears of the spinal fluid. Stained smears from petechiae showed gram-negative biscuit-shaped diplococci, and cultures from the blood, spinal fluid, and petechiae yielded meningococci. The icteric index, the van den Bergh reaction and the blood phosphorus and phosphate were all within normal limits; the cephalin flocculation reaction was + + + +.

The history of acute onset with collapse, the purpura, the hypotension (100/50) despite fundoscopic evidence of hypertension, the cyanosis and the septicemia led to the conclusion that the case was one of acute adrenal insufficiency of the Waterhouse-Friderichsen type.

The patient was given 10 cc. of watery adrenocortical extract intravenously immediately, and two intramuscular injections of 10 mg. of desoxycorticosterone acetate each, 1 hour apart. A second 10-cc. dose of cortical extract was given with 1000 cc. of 5 per cent glucose in saline solution. Within the 1st hour, the blood pressure became unobtainable; Cor-

TABLE 2. Summary of Laboratory Data in Reported Cases.

Carey-11	DATE	WHITE-CELL COUNT	NEUTROPHILS	RED-CELL COUNT	HEMOGLOBIN	NONPROTEIN NITROGEN	UREA NITROGEN	CREATININE	SUGAR	SODIUM	POTASSIUM
		$\times 10^3$	%	$\times 10^6$	%	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	meq./l.	meq./l.
Grace, Harrison and Carey-11	40 F	2	96	3.7	78	62.5	—	2.5	200	141.7	5.1
1/25	30 F	2	96	3.7	78	62.5	—	2.5	200	141.7	5.1
	24 F	Pneumococcus	80/50	30	24	10 mg.	—	—	—	—	—
1/28	—	—	—	32.0	—	Sulfapyridine	15	3.1	98	143.0	5.0
1/29	14.0	90	3.8	80	—	—	—	—	—	—	—
1/31	13.6	88	3.9	80	—	—	—	36	0.6 gm.	—	—
1/6	—	—	—	—	—	—	—	—	4.0 gm.	—	—
1/8	7.3	70	3.6	80	—	—	—	—	50,000 units	—	—
1/12	6.4	70	3.7	80	—	—	—	—	5.0 gm.	—	—
1/16	—	—	—	—	11.5	1.0	105	14.3	0 gm.	—	—
1/22	—	—	—	—	—	—	—	—	—	—	—
1/26	—	—	—	—	—	—	—	—	—	—	—
									64.5 gm. Coramine, vitamins K.		

of liver extract. One son had pernicious anemia; the family history was irrelevant.

Temperature on admission was 102°F. The skin had many petechiae, especially over the extremities and a diffuse, purpuric eruption, chiefly over the trunk. The fingers were cyanotic. The pupils reacted to accommodation. The fundi showed minimal arteriovenous nicking. Otorhinolaryngologic examination revealed many mucosal petechiae. The neck was soft. A few fine, moist rales were heard at the base of the lungs. The heart sounds were distant and of poor quality. Aortic second sound was accentuated. There was aortic murmur with maximal intensity over Erb's point transmitted downward toward the apex. The blood pressure was 100/50 and the pulse 120, with a sinus rhythm. Tendon reflexes were hypoaactive throughout. Brudzinsky's sign was present, Babinski's reflex was absent. The patient's reaction was absent.

The patient showed an increase in blood pressure equilibrium with free fluid. The patient showed in the + + test for c., the presentation was 60 minutes. The patient's were 1.3 milliterol.

mine was given intravenously and oxygen administration was begun. Within 5 hours of the initiation of adrenal substitution therapy, the blood pressure had risen and remained near that level for the balance of the hour period. The initial dose of sulfadiazine was given intravenously by infusion at the rate of 7.5 gm. in 5 hours. The patient continued intravenously at the rate of 1 gm. in 4 hours. The patient became conscious.

During the 1st night, the patient was extremely restful and sufficiently irrational to require restraint. The next morning (approximately 12 hours after admission) she was lucid and able to take medication orally. Thereafter she was given sulfadiazine by mouth at the rate of 1 gm. every 4 hours with large doses of bicarbonate of soda. Vitamins B<sub>1</sub> and C were given parenterally in large doses to reduce the purpuric diathesis and to diminish the chances for acutal vitamin C deprivation through adrenal damage. The patient was started on digitalis therapy, not because there was evidence of cardiac decompensation but rather as a precautionary measure in a toxic patient past the age of 60.

After the first day, 5 cc. of cortical extract was given twice daily for 1 week. Vitamins K and C were continued throughout the hospital stay. The sulfadiazine, for which a blood level of 9 mg. per 100 cc. had been established, was continued daily for 10 days at the rate of 1 gm. every 4 hours. The patient (Fig. 1) dropped to normal in 24 hours, but rose the following day to 101.2°F., from which level it fell to normal in 14 days. (It is interesting to note that the temperature followed the discontinuation of the therapy and that, although the cyanosis and

administration of corticosteroids to 140/90 mm. Hg. First 24 hours intravenous therapy was continued.

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purpura subsided relatively rapidly, small furuncles appeared over the lower extremities in petechial areas despite the sulfonamide treatment.)

The blood pressure throughout the 1st week was maintained around 160/90 and during the 2nd week around 140/60, with one drop to 115/45, which occurred 3 days after the cessation of adrenal substitution therapy. For 3 more days, it fluctuated between 115/45 and 135/70, but then resumed its previous amplitude at around 160/90.

Throughout the course of the disease, the urine was negative except for traces of albumin. Within 2 weeks, the sedimentation rate of the red cells was 5 and 30 mm. in 15 and 50 minutes, respectively. Wassermann tests were repeatedly negative, but the Kahn reaction was successively + + + +, + +, + + + +, + + + +, + + + + and + + +. There was a gradual diminution in the white-cell count to 7000, with normal distribution of the various types of cells. The red-cell counts were repeatedly between 3,600,000 and 3,900,000, and the hemoglobin between 78 and 83 per cent. Four days after admission, the nonprotein nitrogen had dropped from 2.5 to 32.0 mg. per 100 cc., and remained normal thereafter. The blood creatinine and blood sugar were not pathologically altered on any of a number of serial examinations. The

The finding of relatively normal serum sodium, potassium and chloride levels is not astonishing in view of the work of Loeb, Atchley, Benedict and Leland,<sup>23</sup> who observed that even when total adrenalectomy was performed in animals the daily rate of the reduction in sodium was as little as 2.3 milliequiv. per liter. Other workers have noted that alterations in electrolyte levels may be relatively small, even in cases in which there is definite Addison's disease.<sup>21</sup> This patient showed the marked elevations in non-protein nitrogen and creatinine that are generally manifest in Addison's disease during crisis. Since dehydration was not present, this finding emphasizes the close functional connection between the kidney and the adrenal cortex.

The + + + + cephalin flocculation test indicated an active process in the parenchyma of the liver.

TABLE 2 (Continued).

DATE	CHLORIDE	PHOSPHORUS	CHOLESTEROL TOTAL	ESTERS	ICTERIC INDEX	VAN DEN BERGH REACTION	CEPH. FLOC. TEST	PHOSPHATASE	PROTEIN	A-G RATIO	SPINAL FLUID
	mg./l.	mg./100 cc.	mg./100 cc.	%				B.u./100 cc.	gr./100 cc.		
/25	94.2	3.3	122	46	5.0	0	+ + + +	4.0	6.0	2.0	Cloudy (many polymorphonuclears); pressure, 300 mm.; globulin, + + + +; protein, 880 mg. per 100 cc.; chloride, 670 mg. per 100 cc.; culture, positive for meningococci.
28	96.8	—	—	—	—	—	—	—	—	—	Slightly cloudy (318 cells per cu. mm.); pressure, normal; globulin, + + +; chloride, 688 mg. per 100 cc.; culture, sterile.
29	—	—	—	—	—	—	—	—	—	—	
1	—	—	—	—	—	—	—	—	—	—	
3	—	3.2	206	70	11.0	Delayed	+	3.8	5.0	1.5	
12	—	—	—	—	—	—	—	—	—	—	
16	102.0	3.7	170	62	5.2	0	+ + + +	5.7	7.0	2.6	
22	—	3.5	210	52	6.0	0	0	4.1	7.0	3.2	
26	—	3.5	206	75	5.5	0	+	3.0	7.0	1.3	

ating blood sugar and the levels obtained at half-hourly intervals after the ingestion of 100 gm. of glucose were respectively 105, 180, 185, 190 and 145 mg. The basal metabolic rates on two occasions were -7 and -4 per cent. The spinal fluid showed a gradually complete recession in the inflammatory process. The icteric index rose to 11 the second week, and the van den Bergh reaction was simultaneously delayed; hereafter, the former was normal and the latter negative. The cephalin flocculation response decreased from + + + + to negative in 4 weeks. The total blood cholesterol increased from an initial value of 122 mg. per 100 cc. with 45 per cent esters to 210 mg. with 75 per cent esters. The serum protein, chloride, potassium and sodium were within normal limits in each of four determinations (Table 2).

DISCUSSION

Hyperglycemia was an unexpected finding in this case. It had been previously observed, however, in an acute hemorrhagic adrenalitis that was proved post mortem.<sup>22</sup> The normal values subsequently obtained and the normal glucose tolerance noted after recovery from the acute episode in this case suggest that a trigger mechanism released adrenalinlike substances during the collapse of the organism, which secondarily elevated the blood sugar.

This was confirmed by the low total cholesterol, a diminution in the percentage of esters and an elevation of the icteric index. Later all these values returned to normal, suggesting the transient nature of the disturbance and the close relation between hepatic, renal and adrenal activity. It is, of course, possible that the icteric index rose as a result of ecchymotic and petechial hemorrhages.

The acute onset of the disease, associated with collapse, the rapid development of the cyanosis, the petechiae and the purpura, and the hypotension, the hypotonia and the hyporeflexia all indicated an acute adrenal insufficiency of the Waterhouse-Friderichsen type. The early and vigorous institution of therapy was responsible for sustaining the patient during the stage of onslaught with depressed or absent adrenocortical activity. Whether adrenal hemorrhage, simple edema or edema with petechial hemorrhages occurred, it is impossible to say. In any event, without therapy the prognosis would have been hopeless.

In view of the present high frequency of meningitis and the surprisingly high percentage of cases developing the Waterhouse-Friderichsen syndrome, it is important that the disease be borne in mind whenever a sudden state of collapse with purpura occurs in meningitis or following a simple sore throat. That 12 cases have recovered under appropriate therapy emphasizes the necessity for early diagnosis and treatment.

#### SUGGESTED THERAPEUTIC ROUTINE

The pathogenesis of the Waterhouse-Friderichsen syndrome and the rather uniform clinical course of the untreated cases afford an unusual opportunity to standardize the therapeutic regime. Certain conditions may be specifically met:

The pulselessness, cyanosis and state of collapse may warrant the use of Coramine, epinephrine or caffeine sodium benzoate, the values of which are probably in the order named. Dosages should be large and should be repeated on indication, although this is usually unnecessary. Such therapy is in no way fundamental, and there are those who doubt its usefulness, but it is believed that in the case reported such emergency treatment was of supportive value while other therapy was being arranged.

The first treatment for the insufficiency of the adrenal cortex should be 20 cc. of water extract, administered intravenously in 500 cc. of 2 per cent sodium chloride solution containing 5 per cent glucose. At least two and a half hours should be allowed for this infusion. As soon as it is well started, 15 mg. of desoxycorticosterone acetate should be given subcutaneously or intramuscularly; 10 mg. should be injected thereafter every eight hours until the systolic blood pressure is persistently above 100. After that, 10 mg. may be given daily until convalescence is well established, with normal temperature, pulse and blood pressure.

The associated infectious process should have vigorous treatment from the start. If the pneumococcus is the offending organism, it is well to begin treatment with penicillin, if available. An initial dose of 15,000 to 20,000 units intrathecally should be followed by 20,000 to 40,000 units intramuscularly every three hours. In the severer cases, the intravenous route may be employed, preferably by the continuous-drip method. It still seems wise, however, to avoid this route whenever possible, since there is some likelihood of producing a further febrile reaction or a thrombophlebitis. If the usually found meningococcus or any other bacterium except the pneumococcus is present, sulfonamide therapy should be vigorously followed. Sulfadiazine seems to be the agent of choice, since it probably penetrates the spinal canal more readily than do any of the others.

An initial dose of 3 gm. of the sodium salt should be given intravenously as a 5 per cent or weaker solution. In any event, not less than half an hour should be required for its administration. Subsequently, 2 gm. should be used every four hours until oral administration is possible, when the dose should be reduced to 1 gm. every four hours. Sulfonamide treatment is not contraindicated by the azotemia present in these cases. Should this treatment fail, penicillin as above described should be tried without delay.

In support of the activity of the adrenal cortex, it is possible that vitamin C has specific value. One of the crystalline preparations for intravenous use should be employed during the period of stupor. Renal loss is decreased by using several small doses instead of a single large one. The total for the day varies in individual cases from 100 to 500 mg., and can be conveniently administered along with the necessary infusions. If the bleeding tendency is great, there is at times a lowered percentage of prothrombin. Whether or not this occurs, vitamin K or a vitamin K-active substance, such as 2-methyl-1,4-naphthoquinone, may be given empirically. The latter is water soluble and may be administered intramuscularly in doses of 1 to 2 mg. daily.

#### SUMMARY

Recovery from the Waterhouse-Friderichsen syndrome is recorded in the case of a sixty-three-year-old woman with a past history of hypertension. Treatment included sulfadiazine and adrenocortical hormone.

Eleven previously reported recovered cases are briefly summarized, particularly in relation to the therapy received.

The improved prognostic outlook for patients with the Waterhouse-Friderichsen syndrome is stressed.

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## CASUALTIES IN THE SOUTH PACIFIC

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**T**WENTY months' duty in the Southwest Pacific gave me the opportunity to see and participate in the care of many war wounded. The first fourteen months were passed in New Zealand, following which a transfer northward brought my unit close enough to the Solomon Islands campaign to receive battle casualties from there by air.

Duty in New Zealand was very pleasant. The country is roughly a thousand miles long and one to two hundred miles wide. It is made up of two large islands, with a narrow strait between. The total population is only 1,600,000. The climate is delightful. It is much like New England, except that summers are cooler and winters are warmer. At the location of the hospital, the average summer temperature was only 15° warmer than the average winter temperature. During the entire year there was only one light flurry of snow, but there were occasional frosts during the winter months of July and August. Fishing and hunting were excellent, but we were too busy to get much time for outings.

The New Zealanders were incredibly hospitable to the Americans. On several occasions, large parties of hospital patients were invited to spend a week or more on convalescent leave at various New Zealand towns. At these towns, we were most hospitably entertained as guests by the New Zealanders in their private homes. With plenty of beefsteak, butter and cream, the patients often gained several pounds during these periods.

In New Zealand, I was first assigned to several weeks of temporary duty with a hospital unit other than my own. This unit had been given for its grounds a large soccer field on the edge of a town. Starting from an empty, level green field, an excellent modern hospital was built and equipped in the short period of four and a half weeks. All the buildings and equipment had been brought from the United

States. The buildings were of prefabricated steel and were admirably suited for use in hospital construction. Under the supervision of a Navy civil engineer, the work was rushed to completion by the hospital personnel. During the last few days before completion of the buildings, work was remarkably rapid. I particularly recall supervising the laying of a floor in one of the storehouses the day the patients arrived. After we had started laying floor boards from one end of the building, trucks began to unload supplies onto the floor sections we had completed, before we were halfway down the length of the building. The equipment and supplies were plentiful and of the very best quality.

On the thirty-first day after breaking ground, casualties were received from the cruiser battle that took place off Guadalcanal in early August, 1942. As you will remember, four heavy cruisers were sunk — the *Quincy*, *Vincennes* and *Astoria* and the Australian cruiser *Canberra*.

On August 20, 1942, we received from a United States hospital ship 366 patients, almost all of whom had been wounded in the Solomon Islands engagement of August 7 to 9. Only one patient had died during the week aboard the hospital ship, and only one died at the New Zealand hospital. It was obvious that these men had had excellent care. Dressings appeared clean and neat; plaster casts had been carefully applied to the many fracture cases; even the sickest patients appeared well nourished and not suffering from dehydration. No patient seemed to need immediate surgery. There were many severely wounded patients in the group. Lieutenant George Crile, Jr., of Cleveland, Ohio, published an excellent article on this subject in the March, 1943, issue of the *United States Naval Medical Bulletin*. It was entitled "Experiences of the Surgical Service of the United States Naval Hospital, Auckland, New Zealand, with Casualties from the Initial Solomon Islands Engagement." To give some idea of the relative numbers of various types of injuries among these 366 casualties, Crile's figures are useful. There

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were 114 flesh wounds, 104 compound fractures and 40 second-degree and third-degree burns. There were 11 surgical or traumatic amputations.

The flesh wounds had been treated with sulfanilamide or sulfathiazole powder. Many of the wounds had been débrided and had had foreign bodies removed. We noted in many cases that the flesh wounds that did best were those that had received as initial treatment mechanical cleansing, sulfonamide powder locally and no débridement.

Compound fractures were doing well in closed casts. We were impressed with the excellence of the Orr-Trueta method of treatment. As is generally known, it is much easier for the patient than former methods, for he has few, if any, painful dressings. There is a large saving of gauze and dressing material. This was particularly important when the supply line included several thousand miles of Pacific Ocean. With a large number of seriously wounded patients, there was a tremendous saving of valuable time for the medical officers, who would otherwise have spent long hours on tedious, painful dressings.

After several weeks with the hospital group at Auckland, I went back to the hospital to which I had originally been assigned. During the next thirteen months in New Zealand, we treated many more war casualties. I was particularly interested in burns and was given the assignment of taking care of all burn cases.

The "canned" human plasma with which naval medical units are provided was extremely valuable for treating burns in the early stages. In a base hospital, most of the burns were, of course, not fresh ones, but many patients had been given plasma during the first few hours after injury, and had benefited enormously from it. The few cases of fresh burns that were admitted to our hospital were given large amounts of plasma immediately.

A guest at the hospital, Major J. J. Brownlee, chief plastic surgeon of the New Zealand Army, described to us in detail the methods used in caring for burn cases in England during the German blitz of 1939. At that time, he had been associated with a famous English surgeon, Sir Harold Gillies. Briefly, the English method used in the New Zealand Army was as follows. The burned areas were not débrided. Blebs were not broken. Sulfonamide powder and vaseline gauze dressings were applied immediately after injury. After several days, the patient was put into a full-sized bathtub filled with warm, sterile, slightly hypertonic saline solution. After a few minutes of soaking with the dressings undisturbed, the latter were gently floated off under water. The water in the tub was changed several times until clean. After the bath the patient was lifted out onto a sterile sheet and dried with sterile towels, and vaseline gauze dressings were reapplied. Subsequent dressings were done in exactly the same manner. Masks, gowns and gloves were worn during

these procedures to prevent contaminating the open burned areas.

Immediately after Major Brownlee's talk, a bathtub was installed at the end of a ward on which the burn cases were segregated. An ordinary metal bathtub was raised two feet from the floor, so that its rim was exactly the same height as the top of a wheeled stretcher. This elevation was a distinct advantage in getting the patient in and out of the tub. It also made it much easier to work on him while he was lying there. A seventy-gallon tank was constructed on a five-foot platform beside the tub, with a thermometer on it. By hot-water and cold-water connections, the tank was filled with water at 105°F., and enough table salt was added to make a 1 per cent solution. The tub was carefully scrubbed with soap and water, wiped with Lysol solution and rinsed with saline solution before being filled with the warm salt water.

The saline solution was slightly hypertonic, on the theory that, with a greater osmotic pressure than that of the tissue fluids, exchange would be from the burned areas into the bath. The solution was so nearly isotonic and so near body temperature, however, that there was little discomfort for the patient. In fact, patients were usually reluctant to get out of the bath. With the tub nearly full, they floated comfortably, with only a slight amount of weight resting on the bottom of the tub.

A few patients were received who had been treated with tannic-acid jelly days or weeks previous to admission. The saline bath was extremely useful in soaking off the infected eschars. A patient who had been treated with tannic acid for burns incurred when a destroyer was torpedoed was particularly grateful for the bath. He had extensive burns on the face, ears, trunk, arms and legs. We came to the definite conclusion that, in the light of the present knowledge of the treatment of burns, tannic acid in any form is an inferior method of treatment.

Many cases of severe burns were treated with sulfanilamide wax spray. We used approximately the formula originated by Pendleton at the United States Naval Hospital at Mare Island, California. It is as follows:

Paraffin . . . . .	1000 gm.
Liquid petrolatum . . . . .	250 cc.
White petrolatum . . . . .	150 gm.
Cottonseed oil . . . . .	50 gm.
Sulfanilamide . . . . .	50 gm.
Menthol . . . . .	1 gm.
Camphor . . . . .	1 gm.
Oil of eucalyptol . . . . .	1 cc.

Patients treated by this method were put to bed in a warm room lying on a sterile sheet with the head on a sterile pillowcase. They were covered only by a cradle. A hospital corpsman sprayed the burned areas with warm sulfanilamide wax solution every two hours, using a common Flit gun. The red-cell count of severely burned patients was followed care-

fully, and after the first few days, whole-blood transfusions were given whenever indicated.

Before leaving the South Pacific, we had the opportunity of treating a case of severe burns with gentle-pressure dressings over vaseline gauze, together with a course of penicillin. This method seems to hold great promise of becoming the best way to treat fresh, severe burns.

Third-degree burns were cleaned up as quickly as possible and skin was grafted, using the Padgett dermatome or the Humby knife. Pinpoint grafts were used in cases in which there had been much infection. The Humby knife is an English instrument. It is much like our Blair-Brown knife, and is an extremely useful instrument.

All major skin grafts of the extremities were put in plaster casts for seven to eight days after operation. The patient was given 4 gm. of sulfadiazine a day, starting two days preoperatively and continuing until the first dressing was done, a week after operation. This first dressing was always done in the saline bath, after the cast had been removed.

Amputations were, fortunately, relatively few. I recall only one patient who had lost more than one extremity — a man who had lost both feet and one hand. Amputations were mostly surgical, and of the open or guillotine type. They had been done at some point near the front line to prevent infection or for nearly complete severance of the affected limb.

All guillotine amputations were placed in skin traction, using adhesive plaster and a pulley and weight over the foot of the bed. This was, of course, effective in the prevention of retraction of the skin edges. It also provided a much better final weight-bearing stump by lessening the amount of scar tissue and increasing the amount of normal tissue over the end of the stump.

It is extraordinary how little pain a traumatic amputation may cause. An Australian sailor from the cruiser *Canberra* gave me the following amazing story. During the battle in which his ship was finally sunk, there was a tremendous impact as a Japanese projectile struck his ship. He was spun around against a bulkhead but was able to remain in a standing position. He then observed a severed arm lying on the deck near his feet, and said that his first impulse was to feel sorry for its owner. He said that he did not realize that the arm was his own until he recognized a familiar ring on the finger.

Among several cases of penetrating wounds of the chest, I treated only one that resulted in empyema. In most cases there were varying degrees of hemothorax. Aspiration was done only for respiratory embarrassment or for diagnosis in cases of suspected sepsis.

One officer had been shot through the chest by a small-caliber bullet, which had not struck a rib. Three weeks later, when I saw him for the first time, the wounds of entrance and exit had completely healed and he appeared to be symptom-free.

Penetrating wounds of the abdomen were few. One case well demonstrated, however, the importance of meticulous examination after injury by multiple shell fragments. A large fragment had badly fractured the patient's lower jaw, diverting attention to his head. About two weeks after injury, he complained of lower-abdominal pain and inability to void. Careful physical examination showed a recently healed 6-mm. scar in the left side of the abdomen and a deep pelvic abscess. X-ray examination revealed a small particle of steel within the pelvis, which had evidently caused a small, leaking puncture of the sigmoid. The abscess was drained by rectum and the patient recovered.

The subject of foreign bodies is interesting, and we all had considerable experience with them. In one case we counted over 200 of them, mostly tiny, in the back, arms, buttocks and legs. The patient had been standing near an exploding shell on the deck of a cruiser. We came to the conclusion that foreign bodies, unless they cause symptoms or are very large, need not be removed. If they cause infection, lie in joints or cause symptoms by involving vital structures they should be removed.

After fourteen months in New Zealand, I was ordered to a base hospital on an island situated within a few hours by air of the fighting zone in the Solomon Islands. The climate there was entirely different from that of New Zealand. The weather was intensely hot and humid, with a tremendous rainfall. The hospital was well located, however, in a shady coconut grove, on top of a slope where we got whatever breeze was blowing. The natives were of the extremely black type known as Melanesians. There were also many Tonkinese laborers imported during peacetime from French Indo-China to work on the coconut plantations. Tropical diseases were well controlled by careful sanitation. Nearby swamps were drained, puddles were oiled, and natives were segregated from the shore installations, as precautions against mosquito-borne diseases.

Although this island had been notorious for malaria before the war, the sanitation was so good by the time I reached there that one could sit with impunity at an open-air motion-picture show during the evening without fear of dangerous mosquito bites. All hospital buildings were of course carefully screened against insects.

An interesting public-health measure was the picking of all coconuts, from the palms on the hospital compound. This was done because several men had been injured by falling coconuts, and also to avoid having empty coconut shells lying around as breeding places for mosquitoes. Flies, which had been somewhat of a nuisance when we first arrived on the island, were controlled by covering all latrines and garbage.

During the last few weeks of my stay in the South Pacific, penicillin became available in limited quantities. We treated 23 cases, with some improvement in all but 2 cases. One case that failed to improve

was that of a marine who had been shot through the right adrenal gland at Bougainville and had developed a large retroperitoneal and retropleural abscess. He finally succumbed to chronic sepsis and a terminal hemorrhage. The second case was that of a marine who arrived, suffering from a large subphrenic abscess, as a complication of acute appendicitis. He was given penicillin for a week before operation, without improvement. He made a good recovery after 1200 cc. of pus had been drained surgically. It might be added that the abscess cavity on two occasions was washed out with penicillin solution after operation; this may have helped his recovery.

The 21 cases that showed improvement included two patients with suppurative keratitis of the eye, both due to foreign bodies. Both had developed sepsis in the anterior chamber of the eye before penicillin was started. The ophthalmologist considered that their improvement after they were given penicillin was remarkable. Another case was that of a sailor with a septic knee joint of three days' duration, due to a small penetrating stab wound. Without aspiration or drainage, the knee improved rapidly with penicillin treatment. Other cases included a severe burn, a severe furunculosis and several compound fractures due to gunshot wounds.

All the above cases were treated with 15,000 units of penicillin in 15 cc. of 5 per cent dextrose in saline solution, given intravenously every three hours. In most cases this treatment was continued for a week—a total of fifty-six doses. One patient developed a slight phlebitis at the site of the injections, in the antecubital space. The dilution of penicillin was then doubled, giving 500 units per cubic centimeter instead of 1000. The phlebitis then subsided. No other harmful results from penicillin were seen.

Several cases of sulfonamide-resistant gonorrheal urethritis were treated with 20,000 units of penicillin intramuscularly every three hours for five doses. The dilution used was 5000 units of penicillin per cubic centimeter of saline solution. The result seemed extraordinarily good in all cases, although my transfer to the United States prevented an adequate follow-up.

Besides war injuries, there were many cases of the usual peacetime surgical ailments. Appendicitis, hernia, hemorrhoids and infected pilonidal cysts were probably the most frequent ones.

Pilonidal cysts were possibly aggravated by the hot climate and by sitting on hard surfaces, such as wooden benches and jeeps. At operation, a few small cysts that were not badly infected were excised and closed with through-and-through sutures of fine stainless-steel wire. Sulfanilamide powder was applied to the raw surfaces several times during the operation. There was not a large enough series or enough follow-up to draw definite conclusions, but the majority of the wounds closed in this manner appeared to heal by first intention.

The problem of anesthesia was an interesting one in the South Pacific. Pentothal proved extraordinarily useful for almost all types of minor operation. In the heat of the tropical islands, drop-ether anesthesia was somewhat difficult, owing to the rapid evaporation of the ether, but worked perfectly well in spite of this. Spinal anesthesia was usual for laparotomies and major procedures on the lower extremities.

We saw a few cases of filariasis, a mosquito-borne disease endemic in some of the South Sea islands. There appears to be much current rumor and misinformation about the nature of this disease. After having been bitten by an infected mosquito, the patient several months later develops a temporary lymphedema of the arm, leg or scrotum. Elephantiasis may occur as a late complication, but only after repeated infections by new mosquito bites over a long period of years. According to a doctor who spoke at the hospital after three years of peacetime practice in Samoa, a patient with filariasis need not have any fear of elephantiasis unless he remains for many years in the infected area and suffers recurrent attacks. In Samoa, the recurrent attacks of slight swelling due to filariasis are called by the natives "moo-moo." One sometimes hears filariasis referred to as the "moo-moo disease."

The patients at naval hospitals are sailors and marines. As most people know, the United States Marine Corps does not have its own doctors. Navy doctors are assigned to duty with the marines at the front, and hospitalized cases are sent back to naval mobile or base hospitals. The average sailor or marine is young and healthy. These men make excellent patients, with tremendous powers of recuperation. They complain very little and are most appreciative of a doctor's care, when such care becomes necessary. It has been a real privilege to have had the opportunity of taking care of some of these men.

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The above is an account of twenty months' service in the United States naval hospitals in the South Pacific. On account of censorship regulations, most dates, places, numbers and so forth have necessarily been omitted. A few definite surgical impressions that have been gained during this work are as follows:

The combination of mechanical cleansing, sulfanilamide, and immobilization is the best way to treat most flesh wounds, and in wounds so treated, débridement is usually unnecessary and harmful.

Foreign bodies, unless they cause symptoms or are very large, need not be removed.

The Orr-Trueta method of closed-plaster treatment of compound fractures was highly successful.

Burns are best treated by gentle-pressure dressings over vaseline gauze, together with sulfanilamide or penicillin.

## STENOSING TENDOVAGINITIS AT THE

(DE QUERVAIN'S DISEASE)

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**S**TENOSING tendovaginitis at the styloid process of the radius is a relatively frequent disease, but despite this fact it is not well known. There have been but few reports of this condition in the literature since it was first described by DeQuervain in 1895, and it is not discussed in the standard textbooks. Although the disease presents a clear-cut clinical picture, which makes the diagnosis easy, it is often unrecognized by the general practitioner or the industrial surgeon.

The disease is seen chiefly in women. With the present marked increase in the employment of women in industry it is more frequently encountered than formerly. Unless properly diagnosed and treated, its victims are subjected to a prolonged and painful period of disability.

Stenosing tendovaginitis is due to a thickening of the fibrous sheath that covers the tendons and the synovial sheaths of the abductor pollicis longus and the extensor pollicis brevis as they pass through the bony groove in the radial styloid. As the tendons emerge from this tunnel they diverge sharply, the abductor inserting into the lateral aspect of the base of the first metacarpal and the extensor inserting into the dorsum of the base of the proximal phalanx of the thumb (Fig. 1). Because of the divergence of these tendons, considerable tension is exerted on the fibrous sheath on extension and abduction of the thumb. It is thought by some that this tension, exerted repeatedly over a period of time, is the cause of the thickening or stenosis of the fibrous sheath. This may be true, but there is a definite relation between this condition and that of trigger finger or thumb. One in this series of 15 patients has developed bilateral trigger thumbs, and another had been previously operated on for trigger finger. Four have also developed mild symptoms of infectious arthritis. If trauma were the only cause, one would certainly expect to see the condition more frequently in men who do more heavy laborious work. The disease, however, does not often occur in men.

At operation the fibrous sheath, which is about 1 cm. in length, is found to be markedly thickened. At times it is nearly 0.3 cm. thick and has the consistence of cartilage. When the sheath is opened the lining synovial membrane is found to be markedly injected. Free fluid is noted in some of the more acute cases. Usually, however, the synovial membrane is bound down to the tendons by dense adhesions that can be removed only by sharp dissec-

tion. These may be appearance of pannus themselves may present de. the pressure of the stenosed

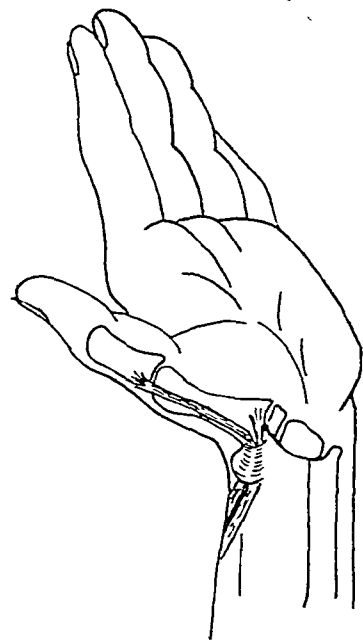


FIGURE 1. Diagram Showing the Location of the Fibrous Sheath at the Radial Styloid and the Divergence of the Short Extensor and Long Abductor on Abduction or Extension of the Wrist.

quently the tendons appear swollen on each side of the point of constriction.

The onset of the disease is usually insidious, without a history of trauma. Symptoms may be present for several months but grow progressively worse. The pain finally becomes so acute as to cause disability. The symptoms may be minimal in the housewife, but become acute if she takes up work that requires the use of the thumbs. Acute cases following a single trauma are sometimes seen. In such cases a past history of mild discomfort on certain motion can usually be obtained. The acute symptoms following a direct blow in these cases are caused by acute edema of a previously thickened fibrous sheath. In other cases they are due to an acute tenosynovitis and not to true DeQuervain's disease.

The disease is seldom seen in persons under twenty-five years of age. It occurs in industry in women whose work requires the use of forceps and in cooks who use heavy pans. Three of the reported

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was that of a marine who had the right adrenal gland, whose chief complaint was developed a large abscess down a clinical thermometer. The abscess. Frequently seen in the housewife, who complains of a tendency to drop things because of pain, and particularly of pain on attempting to wring out clothes.

In the acute stage there is severe pain over the radial side of the wrist joint, especially on motion of the thumb. The pain is localized directly over the styloid of the radius, with radiation into both the thumb and forearm. Any motion of the hand or wrist may be painful, but motions of the thumb, such as active abduction, opposition or acute flexion, as in gripping, are apt to produce the maximum discomfort. The use of forceps or hammers, which require not only gripping with the thumb and fingers but also the use of radial and ulnar flexion, are particularly apt to be painful.

On examination there is sometimes distinct swelling over the radial styloid, but this is not a frequent finding. There is acute tenderness to direct pressure over the radial styloid and over both tendons just distal to the styloid. Active abduction and passive flexion of the thumb cause acute pain at the styloid. Finkelstein\* describes the following test, which is said to be pathognomonic of the disease: the thumb is placed in the palm of the hand, the fingers are flexed firmly over it, and the hand is then forced into ulnar flexion; this causes acute pain if DeQuervain's disease is present (Fig. 2). If the thumb is released, flexion of the fingers with ulnar flexion of the hand is not painful. X-ray examination of the wrist is negative. Ordinarily the above findings are so clear-cut that the condition is not readily confused with any other. Fracture of the scaphoid shows tenderness in the anatomical snuffbox but not over the tendons or the radial styloid. Motions of the thumb are not painful in scaphoid fractures, as in DeQuervain's disease.

Most patients when first seen have had pain for several weeks. All sorts of casts, splints and apparatus have been used. While immobilized, most patients are fairly comfortable; but on removal of the splints and with resumption of work, the symptoms have promptly recurred. In general, conservative treatment is not particularly successful. The acute cases of tenosynovitis are relieved by rest. Rest itself, although it may allow edema of the sheath to subside, does not cause the fibrous thickening to disappear.

The treatment of choice is surgery. The operation is simple and is followed by uniformly good results. Under novocain anesthesia an incision 4 cm. in length is made over the long abductor and short extensor of the thumb. These tendons can be readily identified, since they form the lateral boundary of the anatomical snuffbox. On opening

the thin layer of subcutaneous tissue the fibrous sheath is readily found. The sheath is split with a sharp knife throughout its length and its edges are retracted, exposing the underlying tendons and synovial sheaths. If adhesions are present between the sheaths and tendons, they are excised. It has been my custom also to excise the edges of the fibrous sheath. No attempt is made to close the sheath over the tendons, the only closure required being that of the skin. A compression dressing is applied.

Motion is started on the day following operation. Ordinarily work can be resumed two weeks after



FIGURE 2. Finkelstein Test.

*The thumb is placed in the palm of hand, and the fingers are flexed firmly over it. On ulnar flexion in cases of DeQuervain's disease, acute pain is experienced over the radial styloid.*

operation. There has been no recurrence in this series of cases. Because of the location of the incision and the encouragement of early motion, there has been a tendency for the postoperative scar to be somewhat keloid in type, but the results of surgery have been so satisfactory as to make it the treatment of choice. By early diagnosis and treatment not only is a prolonged painful disability prevented, but many man-hours are saved.

#### SUMMARY

Stenosing tendovaginitis at the radial styloid process is a frequent but seldom recognized condition. It occurs chiefly in women over twenty-five years of age. It is often a source of disability in housewives, particularly those who have recently

\*Finkelstein, H. Stenosing tendovaginitis at radial styloid process. *J. Bone & Joint Surg* 12:509-540, 1930

gone to work in war plants. The true cause of the disease is not known, but trauma plays at least a part in the aggravation or precipitation of symptoms. Once the condition is recognized as a clinical entity, the diagnosis is easy. The condition responds promptly to surgery. Many lost man-hours can be avoided if the medical profession will learn to recognize this disease and to institute proper treatment.

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## MEDICAL PROGRESS

### SYPHILIS (Concluded)

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#### CONGENITAL SYPHILIS

A thorough study of congenital syphilis from the standpoint of fetal autopsy findings has been reported by Dippel.<sup>102</sup> The perivascular tissues of the liver and lungs generally yielded the largest number of spirochetes. Sixteen (24 per cent) of 67 fetuses of syphilitic mothers showed spirochetes in the tissues. It is interesting that 2 of 9 fetuses of Wassermann-negative mothers yielded spirochetes. This is an excellent illustration of the fact that negative serologic findings in the mother are no assurance against congenital syphilis of the child. It bears out the wisdom of the long-held tenet that any woman who has had syphilis should be treated throughout each pregnancy. Spirochetes were not found in fetal tissues prior to the eighteenth week of gestation. It is obvious from this that the syphilitic mother must receive therapy prior to the eighteenth week if her child is to be protected against syphilitic infection. A study of 100 syphilitic mothers and their offspring from a different standpoint has been carried out by Miller.<sup>67</sup> These cases are analyzed from various statistical angles, and criteria for the diagnosis of syphilis of the newborn are described. This author holds that even if all findings are negative in the child of a syphilitic mother, the infant should be re-examined every three months for the first year. It is stated that the child should be closely followed during the first five years of life and that surveillance should be continued to or beyond adolescence. One case is cited in which nothing was found until the child was nine years old. Miller does not believe that syphilis of the placenta can be diagnosed without isolation of the spirochete. X-ray examination of the long

bones has proved unsatisfactory to this author as a diagnostic measure. The last statement is contrary to the opinions of most syphilologists.

The rate for congenital syphilis in infants less than one year of age reported from Scotland for the years 1931 to 1942 inclusive showed a decrease of over 50 per cent.<sup>58</sup> The scheme used in Glasgow for the handling of syphilis in the mother and child is based on the general principle that venereal diseases in these patients should be treated where they are detected. Thus, the pregnant syphilitic woman receives therapy in an antenatal clinic and the congenital syphilitic child is treated in a child welfare clinic. The management of syphilis is thus considered an integral part of maternity and child welfare. Doubtless this contributes greatly toward co-operation on the part of the patient.

What seems to be a most promising report on the treatment of interstitial keratitis has been given by Stone.<sup>69</sup> Vitamin E in the form of wheat-germ oil was used in 10 patients with advanced interstitial keratitis, all of whom had previously received ample antisyphilitic therapy. Four patients had also received artificial-fever therapy. Vitamin E was mainly effective in hastening absorption of superficial and deep corneal exudates; it helped to relieve the associated photophobia and reduced excessive corneal vascularization and circumcorneal congestion. Its administration was carried on over a period of months. In one case, complete clearing of the cornea occurred after eighteen months of vitamin therapy, although only light perception was present in one eye, and perception of fingers in the other, when therapy was begun.

The possibility of confusion between congenital syphilis and scurvy in infants is illustrated in a publication by Levin.<sup>60</sup> A child of fourteen months

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with the typical stigmas of congenital syphilis was thought to have Parrot's pseudoparalysis, although the blood reaction was negative for syphilis. Roentgenologic studies revealed periosteal hemorrhage due to scurvy, with associated rickets. This author found that the majority of infants under six months of age with congenital syphilis have low ascorbic acid levels. He believes that syphilitic infants should be given extremely larger doses of ascorbic acid at an earlier age, since some of the osseous changes ascribed to congenital syphilis are in all likelihood evidence of subscorbutic and subrachitic disturbances.

### THERAPY

#### *Penicillin*

There are innumerable publications on the use of penicillin in infections of all sorts. Its usefulness has apparently been well defined, and it is most fortunately devastating in effect on *T. pallidum*. The action of penicillin on this organism has been carefully studied in vitro and in experimental animals.<sup>61</sup> It became clear from this work that, in the treatment of human syphilis, care must be exercised to administer a sufficient quantity of penicillin to cure the patient rapidly; otherwise there is the possibility of producing a penicillin-resistant strain. In collaboration with the Penicillin Panel, the Subcommittee on Venereal Diseases of the National Research Council, the Army, the Navy and the United States Public Health Service are continuing studies to evaluate the effects of penicillin in the treatment of syphilis. The Army is operating two treatment centers where, under the supervision of specially qualified personnel, early syphilis is being treated.<sup>62</sup> This therapy is being studied from several standpoints, and special procedures have been established to assure a minimum follow-up period of twelve months. The optimum dose schedule has not been determined. Some cases have received as much as 2,500,000 units in a week. The immediate response is excellent, but it should be stressed that no one can foretell the future.

The treatment of early syphilis with penicillin has been continued by Mahoney and his associates.<sup>63</sup> One million, two hundred thousand units in about eight days produced a favorable response in very early infections. An increase in probable failures in patients with secondary syphilis seemed to indicate the need of more vigorous therapy. These authors believe that an increase in the purity of penicillin would effect a distinct improvement in treatment. The development of a method for assaying the spirocheticidal activity of the product would also be of distinct value. They emphasize again that the final value of any treatment for syphilis must await the passage of time. Another group of observers headed by Moore<sup>64</sup> have published a preliminary report of the treatment of 1418 cases of early syphilis with penicillin. Various

treatment schedules were used, and some patients were followed as long as forty-eight weeks. Profound immediate effects were observed—the disappearance of surface organisms from open lesions, the healing of lesions and a trend toward serologic reversal. Relapse appeared to be more frequent after intravenous than after intramuscular injection of comparable doses. The lowest incidence of relapse and the most notable serologic response were in small groups of patients treated with subcurative doses of penicillin and Mapharsen. A favorable effect was also found in early asymptomatic neurosyphilis, acute syphilitic meningitis, early syphilis resistant to routine chemotherapy and infantile congenital syphilis. It was thought that the minimum dose, especially in secondary syphilis, should not be less than 1,200,000 units and that probably it should be more. Herxheimer reactions were frequent but not serious; other reactions were negligible. Smaller groups of patients with early syphilis have been reported by a number of authors with essentially the same results.

Eight clinics were selected for the study of the effect of penicillin on late syphilis, and a total of 182 cases of syphilis have been reported<sup>65</sup>; these were preponderantly neurosyphilis (122 cases) but included benign late syphilis and late congenital syphilis. Benign gummatous syphilis of the skin and bones healed under a relatively small dosage (300,000 units). The abnormal spinal fluid in neurosyphilis was improved to some degree in 74 per cent, and definitely in 33 per cent. The symptoms in neurosyphilis improved less dramatically but to an encouraging extent. The response in interstitial keratitis was varied; at times it was strikingly favorable, but 2 of 14 patients were made distinctly worse. Therapeutic shock effects from penicillin in late syphilis may be serious and should be guarded against by reduced dosage during the first twenty-four hours. It is difficult to evaluate results in miscellaneous groups of cases of late syphilis, and much more time will be required to observe the durability of results.

Still another group of investigators have studied the use of penicillin in the prevention and treatment of congenital syphilis.<sup>66</sup> Although only 14 pregnant women with early syphilis and 9 infants with congenital syphilis were treated, preliminary observations indicate that sodium penicillin has a good effect in both types of case. The limited data seem to indicate that from 1,200,000 units to double that amount, in approximately eight days, is well tolerated by the pregnant woman. Reduced dosage during the first thirty-six to forty-eight hours is advocated. Preliminary results indicate that the infection is controlled and that the infants are born apparently healthy. Here again it is emphasized that the period of observation for either mother or child has not been long enough to be certain of results. The response to treatment with

penicillin was also most encouraging in the congenital syphilitic infant.

Two interesting reports have appeared that emphasize the possibility of partial suppression syphilis by the penicillin therapy of gonorrhea.<sup>67, 68</sup> The amount of the drug used in treating gonorrhea is usually not over one tenth that required in the treatment of syphilis, and may be given within twenty-four hours. It is easily understandable therefore that the treatment of gonorrhea with penicillin may serve to obscure the earliest manifestations of syphilis. The progress of syphilis would not be prevented, and a latent period followed by recurrence or the appearance of late lesions might result. This suggests that, in patients with gonorrhea treated with penicillin, the period of observation for syphilis should be greatly extended.

Although most investigators observed only the Herxheimer phenomenon and a few minor reactions, some reports have appeared that may be warning notes. Hypersensitivity of the tuberculin type has been observed.<sup>69</sup> Urticarial reactions have been frequently observed, and one severe case of urticaria has been described.<sup>70</sup> The occurrence of contact dermatitis from penicillin has also been reported.<sup>71</sup> It is to be ardently hoped that these will not be forerunners of graver systemic reactions to penicillin. One of the remarkable features of this drug has been its comparative freedom from serious deleterious side actions. One cannot help but recall the sulfonamide group, which started out almost as auspiciously but soon came to be regarded with an almost fearful respect because of the reactions accompanying the use of these drugs.

Attention should be called to the fact that penicillin is now available to a limited extent for the treatment of early syphilis in civilians. All cases must be hospitalized, both charity and private, throughout the treatment. An allotment of 1,200,000 units is available for each patient. In Massachusetts this can be obtained from the State Department of Public Health.

There is one point on which complete unanimity of opinion seems to have been achieved by all investigators in the use of penicillin. This is the fact that the results, although encouraging, must be considered preliminary. It is of utmost importance that this fact be universally realized, and it will be extremely unfortunate if the lay press overstimulates the hopes of the public. Although immediate results are comparable with the best of other intensive treatment schedules, this by no means indicates that the *T. pallidum* has been completely destroyed throughout the body. Early recurrence or late sequelae may yet occur. The most careful observations and control of penicillin-treated patients will be necessary over a period of perhaps twenty years before any conclusion can be drawn concerning the ultimate effect. Dosage has so far been purely tentative. The optimum time-dosage

relation has not been worked out. It is obvious then that the penicillin treatment of syphilis must be regarded as an experimental procedure for many years to come. New methods of administration may have to be devised. Penicillin excretion is known to be rapid, which necessitates repeated injections at intervals of three or four hours. A method of renal excretory blockade has been suggested.<sup>72</sup> Thus the action of penicillin can be prolonged and a therapeutic level of penicillin maintained in the blood for a longer time. Methods of slowing and prolonging penicillin absorption from the injection site are also mentioned.

### *Intensive Therapy*

There has been continued study of the rapid intensive administration of chemotherapy for syphilis. A preliminary analysis of results of short courses of triweekly injections of Mapharsen has been published by Eagle.<sup>73</sup> The first 4823 cases so treated are reported. About three fourths of the patients had early syphilis. Two thirds of them were given concomitant weekly injections of a bismuth compound. Triweekly injections of Mapharsen without bismuth gave uniformly poor therapeutic results regardless of dosage. On the basis of observations over a period of fifty to sixty weeks from the beginning of treatment, it is believed that triweekly injections of Mapharsen (approximately 1 mg. per kilogram), combined with weekly injections of bismuth subsalicylate (1.2 gm.) and continued for nine to twelve weeks, probably "cure" 85 to 90 per cent of the cases of early syphilis. The mortality in this series was slightly less than 0.1 per cent, but the authors believe that half these deaths were preventable. There is also a report covering the treatment of 332 cases of early syphilis with massive doses of arsphenamine by the syringe method in a period of five or six days.<sup>74</sup> Three to four injections were given daily. There was a distressingly high incidence of reactions, and grave complications were numerous. The percentage of satisfactory results was comparatively low, and the authors themselves concluded that the method was altogether unpractical. This is not unduly surprising, since it has been long known that arsphenamine is much better tolerated when given slowly in high dilution.

Another study has been reported by the United States Public Health Service.<sup>75</sup> This is an evaluation of massive arsenotherapy for syphilis as carried out in twenty-two co-operating clinics. A total of 4351 patients were treated. Several methods of administration were used, and three arsenical drugs were employed. In one series, typhoid vaccine was combined with multiple-syringe injections of Mapharsen. This group of patients gave the best results, when considered from the standpoint of "cure" balanced against reactions. It was calculated that this should prove effective in 85 to

90 per cent of cases of primary syphilis and in 70 per cent of cases of secondary syphilis. The administration of bismuth during the period of treatment appeared to improve the results. Relapses occurred in about 5 to 6 per cent of the cases of primary syphilis and in 10 to 13 per cent of those of secondary syphilis. Still another series of 487 patients with early syphilis was treated on a five-day schedule.<sup>76</sup> In this group the technic was intravenous-drip therapy with Mapharsen in dosages of from 900 to 1200 mg. In over half the cases bismuth was also given. The treatment fatality rate was 0.76 per cent. Fifteen per cent of all patients followed for five months or longer developed serologic or mucocutaneous relapse. Those receiving bismuth in addition to Mapharsen responded more satisfactorily. The authors estimate that the rate of "complete cure" will not be less than 70 per cent. Additional reports of smaller groups of cases show confirmatory results.<sup>77, 78</sup> The intensive treatment program used by the Army has consisted of forty injections of arsenoxide, given twice weekly, with additional injections of bismuth, covering a total of twenty-six weeks.<sup>14</sup> This system is merely a modification of a former schedule, and the total amount of drug administered (2400 mg.) is about the same. So far the shortened scheme results have been excellent and there has been no increase in toxic reactions.

#### *Combined Fever Therapy and Chemotherapy*

Thomas and Wexler<sup>79</sup> have continued their excellent work with the combination of arsenotherapy and fever. They have tried out several treatment schedules, seeking to avoid the grave reactions that were encountered in earlier work when a one-day treatment had been attempted. The theory back of treatment by this method considers the physiologic effects of fever in the host, which make for increased resistance to the infection, and the direct effect of heat on *T. pallidum*. Although kidney damage was alarming in some of the earlier cases, these authors<sup>80</sup> observed that no noteworthy renal injury was found when the fever produced by physical means was not prolonged beyond five hours. In their last report Thomas and Wexler<sup>81</sup> review two thousand one hundred and forty-four courses of treatment administered to 2023 patients. The great bulk of these patients had primary and secondary syphilis, and the vast majority were treated with Mapharsen and typhoid vaccine. Daily injections of the former in doses of about 1 mg. per kilogram of body weight and four fever sessions induced by the latter in a ten-day period produced optimum results with a minimum of reactions of any sort. Among patients followed for six months or more after treatment, about 80 per cent showed satisfactory results; if retreatments are included the satisfactory results are 85.6 per cent.

An improvement in the use of typhoid vaccine to produce fever has been reported by Solomon and Somkin.<sup>82</sup> This technic consists of the introduction of a high dilution of typhoid vaccine via intravenous drip infusion. By this means therapeutic temperature levels were reached and sustained for several hours. A simplification of this method has more recently appeared.<sup>83</sup> Lawrence<sup>84</sup> has applied the technic in 10 patients who were presumably immune to typhoid bacilli. Ten times the amount of typhoid vaccine originally recommended was employed with satisfactory results. Mapharsen was given at the height of the fever, and bismuth was administered twice weekly on afebrile days. It should be noted that some of the advantages of the use of typhoid vaccine to produce fever are the comfort of the patient, the freedom from a feeling of increased body heat and restlessness, which patients experience in cabinet treatments, and the avoidance of the need of supportive therapy. The mental state of the patient is also unaffected. Cohen and Hale<sup>85</sup> have likewise reported on the clinical application of this continuous intravenous-drip technic with typhoid vaccine. Its more effectively regulated fever is a particular advantage. It also appears to be therapeutically effective in producing fever in malaria-resistant cases. Another publication on the one-day treatment of syphilis with fever and Mapharsen is available.<sup>86</sup> The results were encouraging, but the series was comparatively small.

The use of malaria in the production of artificial fever in the treatment of syphilis has not been abandoned, in spite of the preponderance of reports concerning other methods of hyperpyrexia. Dattner, Thomas, and Wexler<sup>87</sup> treated 419 neurosyphilitic patients with malaria followed by some form of chemotherapy; of the 424 courses of treatment, 148 consisted of routine chemotherapy, and 276 of a daily injection of Mapharsen for ten days before leaving the hospital. No special differences were noted in the results of the two groups. Much time was saved in the cases in which the ten consecutive daily injections of Mapharsen injection were used. Nearly all forms of neurosyphilis were included in the series. On the basis of the spinal-fluid findings, examinations made six months or more after completion of treatment showed "satisfactory" results in 85.9 per cent. From a clinical standpoint the outcome was less satisfactory but nevertheless encouraging. An interesting survey of twenty years' work in the treatment of neurosyphilis has been published by Nicole.<sup>88</sup> In a series of 604 patients, 424 were treated with malaria, the intramuscular method being preferred. In 81 patients, a second attack of malaria was successfully induced, and in 15, a third attack was produced. This author believes that reinoculation attained improvements that could not have been secured by any other means. Recoveries were obtained even in acute and advanced cases, and the addition of chemotherapy led to a higher

recovery rate. A comparatively new pentavalent arsenical, Aldarsone, has been used in conjunction with artificial fever in a small series of patients.<sup>89</sup> The results compare favorably with those of combined artificial fever and Mapharsen therapy. Earlier use of this drug had indicated fewer ophthalmologic complications than those encountered with tryparsamide. In the present series, eye complications were observed in nearly 10 per cent of the patients, which is not encouraging.

#### *Routine Chemotherapy*

A comprehensive study of the results of routine treatment of 5326 patients with latent syphilis over a twenty-year period has been reported by Discker, Clark, and Moore.<sup>90</sup> Of this group there were 926 who were observed for five years or longer and who had a complete physical re-examination at the end of this observation period. Six hundred and thirty (68.0 per cent) had what was considered satisfactory results; an additional 239 (25.8 per cent) were considered probably satisfactory outcomes. The latter were those in whom there was an absence of clinical progression but in whom no re-examination of the cerebrospinal fluid was obtained. These two groups comprised 93.8 per cent of the total number observed. Although this study reports a random sample of the total group, the authors believe that their findings strongly indicate that patients with latent syphilis do extremely well irrespective of the type of treatment received. The optimum amount of therapy to reduce progression of latent syphilis to a minimum is considered to be approximately twenty injections each of an arsenical and a heavy metal.

For some years sulfarsphenamine has been held in gross disrepute by syphilologists for all purposes except the treatment of early congenital syphilis. An interesting study has been reported comparing the toxic manifestations of neoarsphenamine and sulfarsphenamine.<sup>91</sup> A clinic of the United States Public Health Service was utilized for this work. A total of nearly seventeen thousand intravenous injections were given over a period of eighteen months; slightly more than half this number were neoarsphenamine, and the remainder sulfarsphenamine. The reaction rate for neoarsphenamine was so little less per thousand injections than that for sulfarsphenamine that it was considered of no statistical significance. Laboratory investigations indicated that sulfarsphenamine is definitely more stable than neoarsphenamine and apparently more active treponemically. This work suggests that the use of sulfarsphenamine deserves more study.

A new series of bismuth compounds has been isolated, and one in particular, dihydroxypropyl bismuthate, has been studied pharmacologically and clinically.<sup>92</sup> The bismuth is not present as a free ion and does not coagulate and precipitate protein. It is stable in solutions ranging from mildly acid to

extremely alkaline in reaction. This allows it to pass through the stomach and remain soluble in the normally alkaline intestinal fluid, making intestinal absorption possible in amounts previously unattainable. Oral administration may thus produce a high and uniform blood level of bismuth, comparable to that obtained in standard intramuscular therapy. Compounds of this bismuthate series are also suitable for intramuscular injection.

#### TREATMENT REACTIONS

The use of crude liver extract in the prevention and relief of toxic manifestations of arsenical or heavy-metal therapy has been studied by Astrachan.<sup>93</sup> In a group of 52 patients with various systemic disturbances, previous histories of intolerance to drugs, skin eruptions and other complicating conditions, 47 were distinctly improved with the use of liver extract as a supportive measure. In all cases, arsenic or the heavy metal was tolerated when supportive liver-extract therapy was administered. In cases in which liver was used as a preventive measure, injections were given fifteen minutes before the arsenical or heavy metal was administered. Patients with gastrointestinal disturbances were the most markedly benefited.

In view of the serious renal complications that may be encountered with intensive therapy of early syphilis, it seems of value to point out that there is a type of nephrosis that may be associated with untreated early syphilis. An excellent example is reported by Klein and Porter.<sup>94</sup> Syphilis was not recognized as the cause of nephrosis in this case until a typical secondary eruption appeared several days after admission to the hospital. The blood serologic reactions were positive for syphilis. After the first injection of Mapharsen there was a rapid improvement in all symptoms.

Visual impairment during tryparsamide therapy has been discussed by Potter.<sup>95</sup> In so-called "chronic reactions," this author does not believe that the dose of the individual injection, the number of injections or the length and number of courses of injections are associated with visual effects in a consistent manner. The subjective reaction of flashes, sparks or spots before the eyes, together with visual distortion and slightly decreased central visual acuity, is said to occur in 5 to 10 per cent of patients receiving tryparsamide therapy. Objective changes are found on examination in 4 to 5 per cent of patients, with permanent unfavorable results in about 1 per cent. This type of reaction consists of contraction of the visual field and moderate depression of central vision. All these symptoms are classified as chronic, and the prognosis for the restoration of vision is good if the drug is promptly withdrawn. Acute reactions, on the other hand, usually occur prior to the fifth injection and are characterized by rapid deterioration of both central and peripheral vision. The exact nature of the reaction to

tryparsamide remains obscure. It is emphasized that close ophthalmologic observation during treatment is vital and usually provides adequate warning of impending disaster. The same author<sup>96</sup> has also described 4 cases of acute visual reactions among 500 patients receiving tryparsamide therapy, an incidence of slightly less than 1 per cent. The cases described are typical, and it is emphasized that the prognosis is only fair, regardless of treatment.

Anwyl-Davies<sup>97</sup> reports a survey of postarsenical jaundice and dermatitis occurring among a group of 3422 male patients over a period of thirteen years. About two thirds of these patients received neoarsphenamine, and the remainder Mapharsen. The neoarsphenamine-treated cases were complicated by jaundice more than twice as often on a percentage basis and developed dermatitis nearly six times as frequently as those receiving Mapharsen. This author is of the opinion that most of the post-arsenical reactions are due to decomposition products or to toxic substances occurring in the manufacture of the organic arsenicals. Additional factors, such as the use of alcohol, starvation and respiratory and renal diseases, are considered to be possible contributory influences in jaundice.

The United States Navy statistics for the year 1942 are interesting in respect to arsenical dermatitis.<sup>98</sup> Dermatitis comprised 49 per cent of the total reactions for that year. The incidence of arsenical dermatitis in each series of doses was 0.014 per cent. Premonitory signs occurred in 5 of the 17 cases observed.

Some of the complications of artificially induced fever in the treatment of syphilis of the central nervous system are discussed by Etter.<sup>99</sup> The more serious ones are hemorrhage, circulatory collapse and heat stroke. Minor complications include apprehension, restlessness, herpes simplex, nausea and vomiting. The author believes that the routine administration of dextrose by mouth and parenterally before treatment and oxygen continuously during all fever sessions prevents most complications. Additional fluid or dextrose may be required during treatment. The serious complications may require immediate termination of the fever. Winters<sup>100</sup> points out that therapeutic artificial fever may cause temporary or permanent injury to the male sexual organs. Herpetic lesions of the cornea have been reported during mechanical fever therapy<sup>101</sup>; 9 of 25 patients were demonstrated to have superficial punctate keratitis, some being moderately severe.

#### SUMMARY

From the public-health standpoint, there is room for considerable optimism in the reduced incidence of syphilis both among military personnel and among the civilian population. This is all the more remarkable in view of the fact that it has been ac-

complished during time of war. A sobering note creeps in, however, when one considers the gravity of the juvenile delinquency problem. If an increasing percentage of teen-age girls become venders of venereal disease, the foundation of civilization will indeed be undermined. Progress continues in the industrial field; in corporations in which the management proves recalcitrant, the approach may have to be through labor organizations.

False positive serologic tests for syphilis have been receiving a great deal of attention. Improvements in laboratory procedures to identify the false reactions are being attempted, and infectious diseases and other disorders giving rise to false positive reactions have been somewhat more clearly identified.

In the clinical field, certain diagnostic principles that can easily slip the mind of a busy physician not dealing continuously with syphilis are re-emphasized. Means for the identification of atypical lesions are pointed out, and the value of such procedures as lymph-node puncture is cited. Much has been written in the past year in the field of cardiovascular syphilis, and several of the more useful publications are reviewed. Excellent work has been done in the field of congenital syphilis, and one particularly promising report regarding the treatment of interstitial keratitis with vitamin E, which has seemed quite effective in promoting the absorption of corneal exudates, is cited.

Among therapeutic advances, the results obtained following the use of penicillin are outstanding. This potent drug has become available in greater quantity, and an increasing volume of study is being carried out, with most encouraging preliminary findings. Many phases of its use remain to be determined, the matter of adequate dosage not yet having been established. Other methods of rapid and intensive therapy continue to be improved, the combination of fever therapy and chemotherapy being steadily perfected. Some of the more useful and instructive reports regarding treatment reactions are reviewed.

Although penicillin therapy and some of the massive-treatment programs are perhaps the most dramatic elements of this report, it is imperative to stress emphatically the experimental nature of all this work. It must be constantly borne in mind that ten to twenty years will have to elapse before the ultimate value of any new treatment for syphilis can be accurately determined.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31041

#### PRESENTATION OF CASE

A fifty-five-year-old Greek was admitted to the hospital with severe abdominal pain and vomiting.

Three days prior to admission, after partaking freely of alcohol, the patient was awakened from sleep by severe nonradiating, midabdominal pain, at first continuous but later intermittent and cramp-like in nature. He vomited food mixed with wine-colored fluid, and on one occasion passed bright-red blood by rectum. There were no further bowel movements until entry. There were no chills or fever. A local physician was called, and hypodermic injections were administered for the pain. On the following day the pain diminished but the patient

\*On leave of absence.

felt weak and remained in bed. On the day prior to admission he vomited green material on several occasions, and again immediately before entrance into the Emergency Ward. The blood pressure was said to have been 80 systolic, 50 diastolic.

The patient had had epigastric pain relieved by food and alkaline powders for two years previously. One and a half years before admission, a gastro-intestinal series at another hospital had revealed a constant deformity of the duodenal bulb, which was interpreted as an ulcer. There was no apparent obstruction, the stomach being empty at the end of an hour. A Graham test at that time was negative. He had had an appendectomy eleven years previously.

Physical examination revealed a dehydrated, pale man complaining of abdominal pain. The tongue was dry and coated. The heart and lungs were negative. The abdomen was diffusely tender, but more so in the lower quadrants. There was some evidence of shifting dullness. No masses were felt, and peristalsis was diminished. A rectal examination revealed gross blood on the examining finger but was otherwise negative.

The temperature was 98.6°F., the pulse 76, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

Examination of the blood revealed a red-cell count of 6,950,000, with 13.7 gm. of hemoglobin, and a white-cell count of 6850. The urine had a specific



gravity of 1.020, with a + test for albumin and 2 to 3 white cells per high-power field in the sediment. The serum nonprotein nitrogen was 80 mg. per 100 cc., and the protein 7 gm. The serum chloride was 93 milliequiv. and the carbon dioxide content 32.4 milliequiv. per liter. The blood amylase was 30 units per 100 cc. The prothrombin time was 29 seconds (normal, 18 to 20 sec.).

A roentgenogram of the abdomen revealed distended loops of small intestine in the upper and middle portions of the abdomen. No definite air or fecal matter was seen in the colon.

Immediately following admission a Miller-Abbott tube was passed, but the tip never reached the duodenum. Ten per cent dextrose in water and 5 per cent dextrose in saline were administered intravenously, and the patient was given several transfusions and was placed in an oxygen tent. Peristalsis remained diminished or absent. On one occasion he passed 250 cc. of dark-red blood by rectum. The temperature ranged up to 100°F. Repeated roentgenograms of the abdomen revealed some increase in the number of dilated intestinal loops. With increasing hydration, however, the patient appeared to improve clinically.

On the seventh hospital day, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. ROBERT R. LINTON: It is quite obvious that this patient presents a surgical abdomen, and it is my job to diagnose the cause of it. There are certain things in the history that I believe are of significance. The pain began in the midabdomen; at first it was nonradiating and apparently persistent, but later it became intermittent. Associated with the abdominal pain were nausea and vomiting, but it is not quite clear whether he vomited blood. It says "wine-colored fluid," and presumably there was some blood in the vomitus on the first occasion. Later he apparently did not vomit any blood. Another important fact is that he had passed bright-red blood by rectum before he came into the hospital and after he was admitted to the hospital, which to my mind means that he had some lesion of the gastrointestinal tract that was bleeding.

Of interest in his past history is the fact that one and a half years before admission a duodenal ulcer was shown by x-ray; this apparently responded well to medical treatment. At that time he also had a negative Graham test. Although I do not believe that too much emphasis should be placed on one negative Graham test, we can assume from these findings and history that the gall bladder was negative. He had had an appendectomy eleven years before admission.

The physical examination as written here is unrevealing. The only thing they tell us is that the abdomen was diffusely tender, no masses were felt, and peristalsis was diminished. Plain roentgeno-

grams of the abdomen are, I believe, of considerable help and are something that ought to be routinely done in patients with obscure abdominal lesions, especially those who come in with a history of vomiting; I should like to see the x-ray films.

DR. GEORGE W. HOLMES: These films of the gastrointestinal tract show the characteristic appearance of small-bowel dilatation. In the early films, there is no gas in the rectum or any part of the large bowel, so far as I can make out. In the later ones, there may be a little, but the striking thing about them is the definite evidence of obstruction and small-bowel dilatation.

DR. LINTON: I agree with you that these are typical films of small-bowel obstruction. The obstruction was probably in the midportion of the small bowel, perhaps at the junction of the upper and middle thirds. The Miller-Abbott tube, as you can see, was coiled in the stomach; as so often happens with the Miller-Abbott tube when you want to get it through into the duodenum, it would not pass.

There are certain conditions that one must consider as the cause of this man's symptoms. In reading over the history, the first possibility that entered my mind was a severe gastritis, since he had vomited a small amount of blood and had passed a large amount by rectum. I think that it is possible for bright-red blood that has arisen from the stomach and duodenum to be observed by rectum. Such a condition, however, would not explain this man's condition.

Was he suffering from a bleeding duodenal ulcer? It is my opinion that the history of his having had an x-ray diagnosis of duodenal ulcer is more or less of a "red herring" and plays no part in his surgical condition on entry. It is perfectly possible that he had a duodenal ulcer with a small perforation that had sealed off and that he had paralytic ileus, producing the x-ray picture that you see; but if so, there should have been more evidence of peritonitis than was observed.

Could he have had an acute pancreatitis? That diagnosis probably was considered when the patient was admitted, since they did a blood amylase test, which was within normal limits. The dilatation of the small bowel and the fact that he passed blood by rectum are against the diagnosis of pancreatitis.

Another diagnosis to consider is volvulus of the small bowel, which had produced intestinal obstruction and had resulted in melena, nausea and vomiting. That diagnosis ought to be seriously considered, but in view of the low white-cell count, the chance that he had a volvulus of the small bowel is rather slight.

One thing that I did not quite understand in the laboratory examination was the red-cell count of 6,950,000, especially since on physical examination he was noted to be pale. I wonder if that reading is correct. It could possibly be explained on the

basis of dehydration, which he obviously exhibited when he came in.

DR. BENJAMIN CASTLEMAN: Four red-cell counts are recorded; they are 8.2, 6.9, 6.0 and 5.7 million, respectively.

DR. LINTON: That is interesting.

Could he have had an intussusception? That is extremely unlikely, since intussusception occurs rarely in this age group unless it is preceded by a lesion in the bowel.

Meckel's diverticulum is another condition that produces bleeding from the rectum; but, again, I think that that is rarely seen as late in life as at the age of fifty-five years.

Of course, a malignant neoplasm of the small bowel should be considered. I cannot see that he had any definite evidence of this, except that he had passed blood by rectum, meaning that he must have had an intestinal lesion, and that he had intestinal obstruction. Primary malignant tumors of the small bowel are relatively rare, but they do occur.

Mesenteric thrombosis, either arterial or venous in origin, should be seriously considered. The possibility of its being arterial in origin and having the man survive as long as he did without surgical interference is so remote that I believe it can be ruled out on the basis of the history. Mesenteric thrombosis of venous origin does not produce gangrene of the bowel so rapidly, although it may eventually go on to gangrene as the condition continues to spread and to involve more of the blood vessels of the small intestine.

In view of the fact that we are dealing with a man who had polycythemia and hence a tendency toward vascular thrombosis, it seems to me that the likeliest diagnosis is venous thrombosis of the mesenteric veins, resulting in secondary intestinal obstruction. I fully realize that he had a prothrombin time that was above normal, but I think that thrombosis can occur with an elevated prothrombin time.

DR. EMERSON DRAKE: I might say that about two hours after admission the patient vomited several cupfuls of bright-red blood; this added to the confusion of the picture.

#### CLINICAL DIAGNOSIS

Intussusception?

Carcinoma of colon, with extension to small bowel, producing small-bowel obstruction?

#### DR. LINTON'S DIAGNOSIS

Acute small-bowel obstruction, secondary to mesenteric-vein thrombosis.

#### ANATOMICAL DIAGNOSIS

Double ileoileal intussusception, with added intussusception into cecum.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation Dr. J. Gordon Scannell found a mass in the cecum that proved to be an intussusception of the ileum into the cecum. This intussusception was easily reduced, but that was not all. The part of the ileum that had intussuscepted into the cecum was itself the seat of two intussusceptions, which the surgeon was unable to reduce. When we received the specimen in the laboratory we pulled fairly hard and found an old ileoileal intussusception, which in turn had intussuscepted into a more distal segment of ileum. It was this double intussusception that in turn had formed the intussusception into the cecum, which was reduced at operation.

When the ileum was opened there was, of course, rather severe gangrene of the bowel, and within the first intussuscepted loop was the guilty leader — a submucosal lipoma, which was completely viable. Some of you may recall a case of ileoileal intussusception that we discussed here a month or so ago in which we were unable to find any tumor that might have led the intussusception.\* At that time the suggestion was made that perhaps the gangrene had caused a sloughing off of the initial tumor, which might have been a polyp. Here is a case with three intussusceptions and still the polyp that led the tumor was viable.

#### CASE 31042

##### PRESENTATION OF CASE

A five-year-old boy was admitted to the hospital with headache, listlessness and fever.

Two months prior to admission the patient had a bad cold that was said to have been "almost pneumonia." This lasted about a week, following which he appeared to recover completely. Three weeks before entry he became tired and listless. Whereas he had normally been extremely active, he lost interest in play and eating. Ten days before admission he developed a fever of 102°F., accompanied by nausea and followed in a few days by frontal headache and persistent vomiting. There were no chills, convulsions or paralysis.

The developmental history was normal, and the past history was noncontributory.

Physical examination revealed a thin, poorly developed child responding clearly to questions but lapsing into drowsy stupor when undisturbed. The skin was clear and of good color. The ears and throat were negative. The fundi were normal. Small cervical lymph nodes were palpable bilaterally. The neck was stiff and painful on flexion. The heart and lungs were negative. The abdomen was soft, and there were no masses or tenderness. The

\*Case records of the Massachusetts General Hospital (Case 31021). *New Eng. J. Med.* 232:49, 1945.

Kernig sign was doubtful. The deep tendon reflexes were active and equal.

The temperature was 99.4°F., the pulse 100, and the respirations 24. The blood pressure was 100 systolic, 75 diastolic.

Examination of the blood revealed a red-cell count of 5,220,000, with 108 per cent hemoglobin. The white-cell count ranged from 10,200 to 20,650, with 74 per cent neutrophils. The urine was essentially negative. A tuberculin test was negative in a dilution of 1:1000, but positive at 1:100. Blood cultures were repeatedly negative. A Hinton test was negative.

A roentgenogram of the chest revealed a slightly hazy left lung field but no areas of consolidation. There was no enlargement of the hilar nodes.

A lumbar puncture on admission revealed clear colorless fluid under a pressure equivalent to 250 mm. of water. The total white-cell count was 95, with 70 per cent polymorphonuclears. The total protein was 105 mg. per 100 cc., the gold-sol curve 0012333100, and the Wassermann test negative.

The temperature ranged between 100 and 102°F. Repeated lumbar punctures revealed pressures up to 550 mm., a fluid becoming opalescent and a cell count rising to 350. A sugar determination was 39 mg., and the chloride 567 mg. per 100 cc. Several spinal-fluid cultures were negative, as were smears for acid-fast bacilli. A throat culture revealed a Type 22 pneumococcus.

Sulfathiazole therapy was begun on the sixth day. On the eighth hospital day a neurologic examination revealed a patient difficult to arouse and with dilated pupils, fixed to light. There was no papilledema. The gaze wandered but tended to be directed toward the right. There was a left hemiparesis, with increased tendon reflexes and an extensor plantar response on the paretic side. There was a positive Kernig sign.

Death occurred on the tenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. ALLAN M. BUTLER: From the information in the summary of this case, no definite diagnosis can be made. If a diagnosis of a fatal disease for which no therapy is available is made, one must be sure that all diseases for which medical or surgical treatment might be beneficial and in which the prognosis might be favorable are ruled out.

The sequence of respiratory infection, fatigue, listlessness, moderate fever, nausea, headache and persistent vomiting over more than a few days is consistent with the dissemination of a primary tuberculous focus and the development of tuberculous meningitis, but does not exclude influenzal meningitis, brain abscess or encephalitis.

On examination the mental state of the child and the stiff neck are consistent with a diagnosis of tuberculous meningitis. A positive tuber-

culin test in a child of five, and hence one who has had no contacts at school, suggests continued exposure at home or the ingestion of unpasteurized milk. In this connection, however, it might be remarked that resistance to tuberculosis is relatively good at five years of age and hence the incidence of tuberculous meningitis is markedly less at this age than at one, two or three years. The history as given unfortunately provides no information concerning the presence or absence of continued exposure.

The description of the roentgenogram of the chest is noncommittal. Dr. Castleman has informed me that the films are not available for re-examination here but that they were interpreted as essentially negative.

The spinal-fluid findings are not specific. Before discussing them I should like to ask Dr. Castleman if the patient was given parenteral glucose and if the serum chloride was determined at approximately the time of determining the spinal-fluid chloride.

DR. BENJAMIN CASTLEMAN: Parenteral glucose was given during the period over which the spinal-fluid examinations were made. Sugar determinations on other specimens of spinal fluid were 63, 82 and 64 mg. per 100 cc. The level of serum chloride is not recorded.

DR. BUTLER: This means that the spinal-fluid sugar of 39 mg. per 100 cc. and the other relatively normal spinal-fluid sugar levels do not rule out tuberculous or other bacterial infection. Without the hyperglycemia incident to the parenteral glucose they might have been markedly diminished. The lack of information about the serum chloride concentration deprives the low spinal-fluid chloride of diagnostic significance. The elevated spinal-fluid protein would in itself tend to depress the spinal-fluid chloride. Moreover, continuous vomiting may well have produced a low serum chloride level, which would also result in a low spinal-fluid chloride. The occurrence of 70 per cent polymorphonuclear cells is rare in tuberculous meningitis but not impossible; it is more consistent with a pyogenic infection.

The failure to identify organisms on smear is consistent with encephalitis, brain abscess or tuberculous meningitis. The influenza bacillus may also be missed. The failure to culture organisms is also nonspecific. No mention is made of a film or pellicle in the spinal fluid on standing. Moreover, nothing is said about looking for tubercle bacilli in the gastric juice. If the meningitis were due to a Type 22 pneumococcus, the spinal fluid would have been purulent and the organisms would have been seen or recovered on culture.

Sulfathiazole was not administered until the sixth hospital day. This means that such therapy did not interfere with culture of the spinal fluid. It also indicates that the diagnosis of tuberculous meningitis was not clearly established.

The progress of symptoms is not diagnostic. The repeated lumbar punctures may well explain the absence of papilledema.

The possible diagnoses appear to be tuberculous meningitis, with or without miliary tuberculosis, influenza meningitis, encephalitis and, finally, brain abscess, although the absence of localizing procedures indicates that the attending physicians thought that this diagnosis was not possible.

I shall hazard the diagnosis of tuberculous meningitis, with or without miliary tuberculosis.

#### CLINICAL DIAGNOSIS

Meningitis (? tuberculous).

#### DR. BUTLER'S DIAGNOSES

Tuberculous meningitis.

Miliary tuberculosis?

#### ANATOMICAL DIAGNOSES

Tuberculous meningitis.

Miliary tuberculosis of lungs, liver, spleen, kidneys and bone marrow.

#### PATHOLOGICAL DISCUSSION

DR. CHARLES S. KUBIK: Autopsy revealed tuberculous meningitis and miliary tuberculosis of the

lungs, liver, spleen, kidneys and bone marrow. I should suppose that the listlessness, loss of interest in playing and loss of appetite noted three weeks before entry were the symptoms of more or less generalized miliary tuberculosis and that the onset of meningitis coincided with the development of headache and vomiting.

On examination of the brain the customary findings were observed. There was a subarachnoid exudate that was much more pronounced over the base of the brain and brain stem than elsewhere. Numerous tubercles of the arachnoid and pia could be seen with the naked eye and were later confirmed by microscopic examination. The lateral and third ventricles were enlarged to about four times normal size. The ependyma, particularly that of the third ventricle but also that of the lateral ventricles, was studded with tiny, barely visible tubercles that gave the ependymal surfaces a roughened appearance.

There was also a tubercle, 2 mm. in diameter, of the right cerebral peduncle, which may have accounted for the left hemiparesis. No other tubercles within the substance of the brain were found.

The bronchial lymph nodes were normal. The mesenteric lymph nodes were enlarged, but those examined microscopically showed no evidence of tuberculosis.

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## "MIGHTIER THAN THE SWORD"

ACCORDING to authentic information received by the Regional Office of Price Administration in Boston, hundreds of applications for extra food rations on medical grounds have been signed by physicians of this state, on the supposition that they would be turned down by the Medical Advisory Committee, actuated by more patriotic motives than can be attributed to the original signers. We trust that, although many such applications have repeatedly been filed, the actual number of physicians lending their names to such practices is not large.

One explanation given for this casual attitude toward signed statements is that they were not "sworn to." Fortunately the majority of physicians

still honor their own signatures, considering their word as good as their bond. Probably even physicians who sign false food applications would hardly consider it necessary to appear before a notary in order that a signed letter might be supposed to contain the truth, nor would they think that their checks should be certified before being honored. We are, on the whole, accepted at our own valuation until new evidence indicates the need for a reappraisal.

Rationing of the necessities of life in the critical years through which we are passing is a bitter reality that comes hard to a self-willed and indulgent people, a people who have yet to learn whether it really merits the freedom that is supposed to be the reward of victory. Special confidence has long been placed in the physician, who has held a place in our social and economic structure that would hardly be conceded to a mere vendor of nostrums or a peddler of pills. Paid or unpaid, he is, as Wendell Berge\* recently indicated, a particularly esteemed public servant. The public and the nation have a right to expect that he guarantees the honesty of any document to which he affixes his name.

## MEDICAL PREDICTIONS

IN TWO previous editorials<sup>1, 2</sup> the *Journal* expressed disapproval of the policy of the *Reader's Digest* in publishing articles<sup>3, 4</sup> that tend to misinform and mislead the public. Those opinions still stand for implications made in an article, entitled "Atabrine Fully Vindicated: Malaria, scourge of mankind, *can* be licked," appearing in the December, 1944, issue of the same periodical.

Incidentally, the current article indicates that the author has now learned that mosquito control is a major part of malaria control. Furthermore, it contains scientific evidence for his previous predictions. The major part of this evidence, however, has accumulated since 1942 through the combined labors of medical officers in the armed forces and the concentrated research of pharmacologists and malariologists. Fortunately, these medical men and scientists did not spend their time in making arm-chair predictions of things to come.

\*Berge, W. Justice and future of medicine. *New Eng. J. Med.* 231: 721-729, 1944.

Although the great amount of field and laboratory experience gathered in the last two years has taught us how to use atabrine safely and more effectively, the fact still remains that this drug will not prevent infections, effect radical cures or prevent relapses in a certain percentage of men infected with tertian malaria. One cannot help but wonder what the men in the armed forces who contracted relapsing tertian malaria in the South Pacific and the medical officers who treat them have to say about the curability of malaria. Since tertian malaria produces the bulk of morbidity among people in endemic areas, the validity of the statement that "malaria can be licked" by atabrine, or by any other known drug, does not stand up to critical examination.

Endemic areas of malaria will continue to exist just so long as relapses occur to provide a seed bed of gametocytes for local anopheline mosquitoes to transmit the infection to a healthy person. Since the use of known drugs cannot prevent relapses and since modern mosquito control cannot entirely eliminate the anopheline vectors, the possibility of malaria epidemics persists. Furthermore, the elimination of malaria from the world, unfortunately, is not dependent on the cost of a dose of an antimalarial drug, of a mosquito repellent or of a lethal insecticide. The problems of malaria, venereal disease, respiratory disease and malnutrition, to mention a few of the significant menaces to public health, are firmly linked with the economic and intellectual welfare of the people.

Finally, the article under discussion criticizes the National Research Council and its committees for lack of faith in atabrine early in the war. It should be pointed out that the function of a group of medical advisers is not idly to predict that this or that drug will eradicate this or that disease. Their responsibility is to protect and save the lives of people on the basis of their judgment in obtaining and evaluating evidence for or against the use of a drug, serum or vaccine, a method of treatment or a surgical operation. Lives of people — our boys — are at stake, not merely the circulation of a magazine.

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## MASSACHUSETTS MEDICAL SOCIETY

### EXECUTIVE COMMITTEE OF THE COUNCIL

On December 27, 1944, the Executive Committee of the Council, on the recommendation of the Committee on Membership and representatives from the supervising censors, took the following actions:

Allowed the following named fellows, applying for retirement and with all dues paid and in good standing, to retire under the provisions of Chapter I, Section 5, of the by-laws, such retirement to be effective as of January 1, 1945:

Alley, Ernest J. (Middlesex North), Billerica.  
Estabrook, Charles T. (Worcester), 10 Algonquin Road, Worcester.  
Painter, Charles F. (Norfolk), 520 Commonwealth Avenue, Boston.  
Pease, Lewis W. (Norfolk South), 135 Webb Street, Weymouth.

Allowed the following named fellow, applying for retirement, to retire with remission of dues owed the Society under the provisions of Chapter I, Section 5, of the by-laws, such retirement to be effective as of January 1, 1945:

Miller, Samuel O. (Hampden), 73 Ellsworth Avenue, Springfield.

Reinstated the following named physicians, who had resigned from the Society while in good standing, under the provisions of the by-laws, Chapter I, Section 10:

Hatt, Ednah S. (Hampden), 720 Longmeadow Street, Longmeadow.  
Woodman, Alice J. Hopkins (Plymouth), Standish Street, South Duxbury.

Reinstated the following named physicians, under the provisions of Chapter I, Section 10, of the by-laws, who had been deprived of fellowship for the nonpayment of dues, provided their arrears in dues at the time they were dropped plus the dues for 1945 be paid to the treasurer of the Society:

Canzanelli, P. (Middlesex South), 300 Mt. Auburn Street, Watertown.  
Ginsberg, Max (Essex South), 70 Washington Street, Salem.  
Healy, John F. (Norfolk), 374 Dudley Street, Roxbury.  
LeBeau, Raoul J. (Worcester), 154 Main Street, Spencer.  
Manoogian, B. J. (Essex South), 5 Holten Street, Peabody.

Remitted the dues owed the Society of the following named fellows, who are ill and incapacitated, under the provisions of Chapter I, Section 6, of the by-laws:

Keay, Harry C. (Worcester), Clinton Road, Sterling. 1942, 1943 and 1944.  
Sweeney, William J. (Middlesex East), 4 Avon Street, Wakefield. 1944.

Allowed the following named fellows to change their membership from one district society to another, without change of legal residence, under the provisions of the by-laws, Chapter III, Section 3.

Butler, Allan M., Massachusetts General Hospital, Boston (Norfolk to Suffolk).  
 Park, Francis E., 172 Commonwealth Avenue, Boston (Middlesex South to Middlesex East).  
 Quinby, John T., 226 Marlboro Street, Boston (Norfolk to Suffolk).

The personnel of the Committee on Membership is as follows: Harlan F. Newton, *chairman*; John E. Fish, Peirce H. Leavitt, Sumner H. Remick and Samuel N. Vose. The representatives of the supervising censors are as follows: William H. Allen, H. Quimby Gallupe and Albert E. Parkhurst.

MICHAEL A. TIGHE, M.D., *Secretary*  
 Executive Committee

## DEATH

SISKIND — Alexander L. Siskind, M.D., of Lawrence, died May 5. He was in his seventy-eighth year.

Dr. Siskind received his degree from the College of Physicians and Surgeons, Boston, in 1890.

## WAR ACTIVITIES

### INDUSTRIAL HYGIENE

#### SICK ABSENTEEISM AND MEDICAL CERTIFICATES FOR INDUSTRIAL WORKERS

The present critical need of manpower for increased war production calls for more effort to be directed toward reduction of unnecessary absenteeism and labor turnover. Among the many factors bearing on this problem is the relation between private physicians and industrial physicians. A statement recently prepared on this subject by the Safety and Security Division, Office of the Chief of Ordnance, Army Service Forces, directed toward industrial physicians in ordnance plants, has been called to our attention because of its applicability to all plant physicians and co-operating private physicians.

This statement says, in part: "To minimize absenteeism alleged to sickness and terminations attributed to ill health, the closest possible co-operation should be maintained between plant physicians and private physicians in nearby communities. Private physicians often have no accurate information concerning health hazards associated with their patients' jobs in ordnance plants and the generally satisfactory medical and engineering measures taken for their control, and are often at a loss as to how to advise their patients regarding complaints related to work. Likewise, private physicians are not generally aware of the information concerning their patients, available from the plant physician in connection with past examinations, blood tests, x-ray findings and other diagnostic aids."

The related problem of medical certification of illness has also been brought to our attention as a matter that should be considered by the state industrial-hygiene divisions. This subject was discussed in an editorial entitled, "Medical Certificates and War Production," published in the *Journal of the American Medical Association*, issue of November 11, 1944. The private physician's responsibility is presented in this editorial as follows: "The Government and its contracting agents customarily require medical certificates to cover an absenteeism alleged to illness or a labor termination attributed to reasons of health. The medical profession is then put under pressure by thoughtless persons who see little harm in collecting disability benefits or in obtaining better jobs on pretext of illness. They fail to see the cumulative results of hundreds of thousands of such acts on critical war production. Responsibility rests squarely on the physician to act as prosecutor, defense attorney and judge before issuing such a certificate. He fails himself, his profession and the war effort if certificates are issued without due cause."

Traditionally, the doctor has been called on to champion and to be an advocate of his patient. In the main, the patient has been the one who employed him and he has instinctively defended the patient against any or all groups having impersonal interests. The doctor is called on to certify to this and to that. He must certify birth and death; the occurrence of contagious disease; the health of food handlers; and the freedom from disease of candidates for marriage. Health and accident policies depend to an appreciable extent on the knowledge and integrity of practicing physicians. Compensation statutes require medical judgments as bases to support legal judgments. One easily understands why the busy doctor labels all certification a "chore." It is true that to refuse to sign any statement his patient requests, the physician risks an irate individual, but one wonders what degree of confidence and respect the patient will have in his doctor if the latter, unwittingly or not, falls in with such a procedure to circumvent common honesty.

The tendency of some workers is to indict fumes, gases, dust and so forth for real or alleged ill health. Actually, few unskilled workers know what if any occupational hazards exist in their working environment. Such a worker, in the role of a patient, may influence the family doctor to a most astounding and untenable diagnosis. It seems opportune to urge that physicians protect themselves in this respect by using confirmatory sources of information.

State and local industrial-hygiene divisions can give the private physician information on the specific environmental health conditions in a particular plant on request, when there is any question concerning the possibility of illness being incurred on the job. They can also assist industries in developing a standard form of certificate for physicians to use in making reports and can bring this subject to the attention of medical societies as opportunity offers. Reprinted from *Industrial Hygiene News Letter* (December, 1944).

## NOTICES

### BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the Thorndike Amphitheater of the Boston City Hospital, on Wednesday, January 31, at 12:00 m. Dr. George W. Harley will discuss "Twenty Years of Tropical Medicine in Liberia."

### NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, February 1, at 7:15 p.m. in the classroom of the nurses' residence. Dr. Pauline Luzackas will speak on the subject "Torticollis."

### NEW YORK INSTITUTE OF CLINICAL ORAL PATHOLOGY

The New York Institute of Clinical Oral Pathology will hold its one hundredth monthly conference at the New York Academy of Medicine on Monday evening, April 30. Members of the medical and dental professions will discuss the subject "A Survey of the Antibiotic Problem," both from the theoretical and from the clinical standpoints.

Members of medical, dental, public-health and other professional groups are cordially invited. For further information all communications should be addressed to G. Roistacher, Executive Secretary, 101 East 79th Street, New York 21, New York.

(Notices continued on page xxi)

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## THE USE OF THE TERM "PSYCHONEUROSIS"

LIEUTENANT COLONEL JACKSON M. THOMAS, M.C., A.U.S.\*

MANY men and women discharged from the Army for medical reasons have been classified as neuropsychiatric cases. This fact and the trend of statistics in medical journals, newspapers and magazines pertaining to war neuroses suggest that it would be unfashionable today not to show alarm at the rate soldiers are developing nervous disorders. History discloses, however, that there is a similarity between the widespread concern over the conditions generally described as psychoneuroses and the ill-founded apprehension voiced by Beard<sup>1</sup> in 1881, when he declared:

All this is modern and originally American; and no age, no country and no form of civilization, not Greece, nor Rome, nor Spain, nor the Netherlands, in the days of their glory, possessed such maladies. Of all the facts of modern sociology this rise and growth of functional nervous disease is one of the most stupendous, complex and suggestive.

These words refer to conditions that Beard included under the appellations "nervous exhaustion," "neurasthenia" and "American nervousness"—terms that, like Charcot's "*grande hystérie*" and Morton Prince's "multiple personality," cause a false alarm in psychiatric circles similar to that felt by some psychiatrists with reference to psychoneurosis. That many American soldiers have been judged to be victims of this malady and that the facilities of the Veterans Administration are being organized to care for numbers of neuropsychiatric cases are a matter of record and tend to make it difficult to believe that the wolf of psychoneurosis is not at the door this time. On the other hand, if the manifold conditions under which this war is being waged are borne in mind, it seems reasonable to ask what normal reactions under these ordeals might be. Alternating between battling a cunning and skilful enemy and contending with long periods of idleness, homesickness and boredom in the cold of the Arctic, in the heat and disease of the tropics and in the dust of the desert puts every man's emotions under a strain. Add to these factors delays in the delivery of mail or, still worse, the arrival of letters and hometown newspapers in which the soldier is told that the people back home are con-

tinuing to motor to Florida in the winter and to the Berkshires in the summer, and the soldier may be granted a variety of emotional reactions in his foxhole. Some of these will be psychoneurotic and others psychotic in nature, for experience has shown that in any large organization of men a certain percentage inevitably manifest mental disorder. Others, however, will be mere responses to the situation—unlinked to unconscious factors to which one is accustomed to attribute the symptoms of functional nervous disorder.

From a psychopathologic point of view, the psychoses that I have seen in this war have not differed from those observed in a busy psychopathic hospital in peacetime, except in the subject matter of the delusions and hallucinations, which vary, as they have throughout the ages, with the contemporary topics of preoccupation. This statement holds true for that group of cases regarded as acute schizophrenias, which some psychiatrists think are peculiar to this war. These cases, characterized by short periods of confusion, transitory delusions and hallucinations and quick recovery soon after admission to a hospital, are closely similar to the clinical states of emotional turmoil to which Campbell<sup>2</sup> often called attention. They vary from the latter only in that the subject matter of their pathologic beliefs is more often concerned with factors prevalent in a man's thoughts in time of war. The way the patient deals with these factors, however, in war or peace, depends on the same mental mechanisms that the normal mind utilizes in adapting itself to any condition of stress.

The practical disposition of psychoses in the Army is clear-cut. Experience has shown that the majority of these patients should be discharged from the service. Some of the psychoses instigated by infective and exhaustive states, which clear up when the organic, debilitating processes subside, are exceptions to this general policy.

A widespread misuse of the term "psychoneurosis" in the present war has made the treatment and disposition of cases placed in this diagnostic classification more complex than that of the psychoses. Some of the difficulty is due to the fact that the psychiatrist is too often unfamiliar with the life of

\*Associate in psychiatry, Harvard Medical School, and superintendent, Channing Sanitarium, Wellesley, Massachusetts (on leave of absence).



a soldier in the field. Imbued with theories of abnormal human behavior, remaining within the wards of a hospital and feeling the necessity to fit every record into the prevailing order of a psychiatric system, he runs the risk of confusing signs of boredom, homesickness, reactions against discipline and the normal apprehension that many excellent soldiers experience before going into battle with symptoms of a true psychoneurosis. The borderline between normal reactions to difficult situations and emotional states that are to be regarded as symptoms of an ominous personality disorder is sometimes a narrow one. Human nature is not a standardized affair. Normal men differ in their output of energy and in their medium of self-expression. Some are more sensitive than others in dealing with their diverse inner needs and with the complex demands of military life.

The discussion of issues involved in some of the equivocal states of mind attributed to psychoneurotic mechanisms in this war may be clarified if attention is focused on concrete case histories. To this end I shall confine myself to descriptions of cases that I have examined.

**CASE 1.** A 34-year-old, married private first class, the father of two children, enlisted in the Air Force on September 23, 1942. His childhood had been normal. After completing high school, he attended a business college for 2 years. Thereafter he worked efficiently for 14 years for an electrical company. During that time his health was good. Soon after he enlisted in the Air Force he was assigned to the ground crew of a bomber squadron, with which unit he went to Africa in February, 1943. Early in May of the same year he spent a week in a field hospital because of an unexplained fever. When he returned to his unit, he was assigned to security guard duty at a post in advance of the airfield, to aid in protecting it against surprise attacks by the enemy. In the latter part of that month he began to be troubled by insomnia, anxiousness, spells of crying and "the jitters." He grew melancholy, feared he would never live to see his wife and children again, and deplored the fact that he had enlisted in the service. Thoughts of his family were intensified when he was cautioned to be more on the alert than usual, as a result of a rumor that enemy paratroopers had descended in the proximity of his post. The "jitters" increased, but he continued to perform his duty until July 23. On that date he reported to his unit medical officer, who at once sent him to a hospital in Egypt, where a diagnosis of psychoneurosis, anxiety state, was made. He was given Sodium Amytal and kept asleep almost continuously for 2 days. He improved but continued to be nervous and was evacuated to a general hospital some distance from the combat area. On November 11, he reached a hospital in the United States. En route home most of his symptoms disappeared. By December 7 all his symptoms had disappeared. He slept well, did not cry once after setting foot on American soil, was free of the "jitters," and asked to be returned to duty. Questioning disclosed that he had a good understanding of the problems that had troubled him in Africa. He was returned to duty with a diagnosis of simple adult maladjustment.

It is significant that this patient's internal equilibrium was not upset before he entered the Army, nor thereafter until he found himself in the proximity of dangerous combat. Confronted by death and tortured by images of his wife and children on the one hand, and prodded by a sense of duty to his country on the other, he developed the "jitters," cried and could not sleep. Such a reaction incapacitated

him at the time, but I doubt that one would have had to peer into the depths of his unconscious to see that his conflict represented no more than a struggle between an urge for self-preservation and a sense of duty.

**CASE 2.** A 27-year-old, unmarried sergeant entered a general hospital in England in May, 1943, because of a respiratory infection. He had been inducted into the Army in June, 1942, and soon thereafter was assigned to an organization of engineers, with which he arrived in England in February, 1943. His record in the Army was good. Until the time he entered the hospital he had never consulted a medical officer. His respiratory condition disappeared, but in the course of the usual questions pertaining to his medical history, he stated that he sometimes vomited soon after meals. This information led to a complete gastrointestinal study, which disclosed no structural disease. The case was referred to a psychiatrist, who made a diagnosis of gastric neurosis and recommended transfer to a neuropsychiatric hospital. This recommendation was carried out. In that hospital the patient reiterated that he sometimes vomited after meals but added that he was not concerned about the matter since he had occasionally vomited small amounts of food for 2 years before he entered the Army. He was puzzled, however, over the fact that he was regarded as neurotic, and volunteered that he never would have told the medical officer in the first hospital that he vomited if he had known that by doing so he would be sent to a psychopathic hospital. He stated that before he entered the Army he drove a large van regularly over a distance of 500 miles. Along the route he stopped for meals at roadside houses. If he continued his trip immediately after eating, when he had previously driven a long distance, he sometimes found it necessary to get out of the van and vomit part of what he had eaten. Having done so, he continued his trip without further discomfort. According to his statements, this was such a recognized and frequent happening with other drivers that the company physician who examined all drivers every 6 months questioned them specifically about it.

In England, the patient was an efficient driver of a bulldozer tractor. He occasionally regurgitated small amounts of food if he worked hard soon after eating, but he was not concerned about this any more than he had been before his induction, accepting it as peculiar to the type of work he performed. There was no loss of weight. After 3 weeks' observation, during which time the patient regurgitated a small amount of food on only one occasion after breakfast, a diagnosis of no disease was made and he was granted his wish to return to duty.

This case illustrates how a simple vegetative habit, a condition that may have been instigated by the nature of a patient's work, is sometimes thought to be an expression of a psychoneurotic type of conflict of emotions. On the contrary, this patient showed no concern about his gastrointestinal tract. He adapted himself well to civilian life and to the Army. It is unlikely that he would have come to the attention of medical officers but for his respiratory infection.

**CASE 3.** A 29-year-old, married corporal, a mechanic, participated in the invasion of Sicily. His early development was normal. After completing the 7th grade at school he worked at various jobs, finally securing a night position with an express company, which he held at the time he entered the Army. He married at 22 a girl whom he had impregnated. Their marriage was an unhappy one, owing to the wife's not showing the proper interest in the child and having illicit sex relations with other men. The patient was inducted into the Army in May, 1941. Soon after he completed his basic training he was assigned to an Ordnance organization as a mechanic. He showed no signs of nervousness before entering the Army, nor thereafter did he come to the attention of medical officers until July 10, 1943, when he took part in

the invasion of Sicily. On that occasion, as his unit debarked from barges, German artillery and dive bombers opened up with devastating effect and continued to harass the invaders throughout the day. One of the patient's friends was wounded. Fear for his own safety increased. When a bomb fell in a bivouac area and killed many soldiers, he lost control, ran back and forth on the beach, and cried out with terror. This behavior caused him to be admitted to an emergency hospital, where he remained for only a few days. He then rejoined his unit, with which he continued to do duty until the end of July, when trembling, fear, uncontrollable crying and a lack of desire for food led medical officers to evacuate him by airplane to a station hospital in Africa on July 30. Five days later he was sent to duty at a replacement pool. He soon became emotionally disturbed again and was sent to another station hospital, whence he was evacuated to the United States with a diagnosis of psychoneurosis, anxiety state. By the time he had reached a general hospital in this country on November 21, all his symptoms had disappeared. He slept well, showed no signs of anxiety, and attributed his emotional disturbance in Sicily to an inability to withstand combat conditions. He asked to be permitted to return to duty elsewhere as a mechanic, "to regain my self-respect." On December 11, a board of medical officers diagnosed his case as one of simple adult maladjustment and recommended that he be returned to duty other than combat. This recommendation was carried out, and so far as is known he is adjusting well.

The state of mind that this soldier manifested under fire is another example of the emotional turmoil that some men undergo as the result of a conflict between a fear of death and a sense of duty. Although trembling, crying and apprehension persisted after he was removed from the combat area, such was the case only so long as there was likelihood that he would re-enter it.

CASE 4. A 20-year-old, unmarried private in the Field Artillery participated in the invasion of Italy. As in Cases 1 and 3, he had no neuropsychiatric record until the time he entered a combat zone. On September 14, 1943, he was admitted to an evacuation hospital, where a diagnosis of psychoneurosis, anxiety state, severe and manifested by extreme tremulousness, fear and panic reaction, caused by combat, was made. Two days later he was transferred to a station hospital. There he was described as a very shaky, wildly staring, immature, 20-year-old boy with only 7 months' service in the Army. In the early phase of the invasion, German 88's shelled his unit's gun emplacements and during that time the patient was in a constant state of panic; he spent all his time in a foxhole. He could not recall the events of a period of 3 days. He appeared to be "frozen with fright," and whenever he heard a plane he shook violently. The diagnosis of psychoneurosis, anxiety state, was confirmed, and the patient was evacuated to a general hospital in the United States, arriving there on November 21, by which time his symptoms had disappeared. Soon after admission he stated that he felt as well as ever and expressed a desire to return to duty. Later, however, after a furlough to his home, he insisted that he should not be returned to duty because he thought that some of the symptoms he had shown in Italy would return. His attitude indicated a letdown in morale more than it pointed to a persistence of the symptoms for which he had been removed from the combat zone. He was sent to duty in the United States with a diagnosis of simple adult maladjustment.

#### DISCUSSION

The cases that have been described are samples of the emotional states under discussion that are frequently classified with the psychoneuroses. That there are many genuine psychoneuroses detected in the Army for the first time overseas is beyond argument. If, however, one is to retain the generally accepted concept that a psychoneurosis is a nervous

disorder dependent on complicated mechanisms of the mind involving unconscious conflicts, it is difficult to reconcile the reactions exemplified by the case histories cited with this condition. The fear, fright and tremulousness shown in Cases 1, 3 and 4 constitute a behavior pattern that has been witnessed in armies throughout the ages. Until the advent of modern psychiatry, such conduct was attributed to a variation in men's capacity to sever themselves from their usual way of life and to conquer a fear of impending death. The will to fight, morale, training, fatigue, disheartening reverses and leadership were recognized as factors able to influence a man's emotions. These factors are acknowledged in this war, but the frequency with which the diagnosis of a psychoneurosis is made raises a suspicion that psychiatrists have encouraged a shrouding of them in an ill use of terminology. In doing so they have thrown the problem of psychoneurosis out of focus with what seems to be the facts. The prompt recovery of many patients when they are removed from a difficult situation adds weight to this assumption.

I saw patients in England, members of the Air Force, who were in combat over the Continent and others who had not been in combat, and considered them unsuitable for further duty. They were returned to the United States with a diagnosis of psychoneurosis. Before they arrived, I was ordered to report for duty at the same hospital to which they were later admitted. Re-examination of some of these patients disclosed that a remarkable improvement had taken place in them, especially in those who had not been in combat. This observation opened my eyes wider to the haste that I had been guilty of in the use of the term "psychoneurosis." In some cases I had mistaken boredom, homesickness and what the British call "morale lesions" for symptoms of a nervous disorder.

Recent use of the word "anxiety" illustrates further how muddled is the present knowledge of the psychoneuroses. There are psychiatrists who regard the familiar fear of a soldier in a dangerous situation as a measure of the emotion of an anxiety neurosis. This is tantamount to calling all frightened and bewildered soldiers psychoneurotic. There was a time when "anxiety" was considered an appropriate word for the emotion present in clinical states characterized by palpitation, dyspnea, sweating, anxiousness and apprehension. Of late, however, this word has been used so loosely that it has almost acquired buoyant and ethereal qualities. This careless use of the term does injustice to the Army, the soldier and the taxpayer. So does the term "depression" when it is applied to simple nostalgias. These latter conditions were often seen in World War I. When the cause, which was absence from home or some factor related to it, was removed, the patient promptly recovered. Salmon<sup>3</sup> cited cases who recovered on the voyage home, some

doing this so rapidly that a suspicion of malingering arose. Similar recoveries are being seen in the present war. They should allay the fears entertained with regard to some of the erroneously classified psychoneuroses.

It may be argued that a disappearance of anxiety and insomnia under the conditions cited does not constitute a cure, and that the unconscious must be exposed to remove the real trouble. This point of view may be correct for some true psychoneuroses. The tension and anxiety of the cases discussed here, however, seem to have arisen from obviously trying situations rather than from hidden conflicts.

If the reactions under discussion are to be excluded from the psychoneurotic group, it is in order to ask what name is to be given them. The idea that an emotionally upset soldier is not a particular example of a recognized disorder is disturbing to some psychiatrists. Nor does modern warfare permit the outlet that Joshua seems to have had before the siege of Jericho, when it was directed that "the fearful and faint-hearted return unto his home lest his brethren's heart faint as well as his heart."

No one who is familiar with the fleeting fashions in psychiatric nomenclature wants to be caught adding another term to the confusion. Moreover, it is obvious from what has been said that I believe that some of these cases present problems in morale, discipline and stamina. If this is so, it follows that any term connoting a mental disorder will cloud the issue. The answer to the question seems to rest in the prophylactic orientation program now under way—the prevention of states that require a stigmatizing name.

For the patients who reach a hospital, regulations permit the use of the terms "observation—no disease found" and "simple adult maladjustment." The latter term does not always fit the picture, but for the patient returning to duty it is less of a handicap when he reaches his unit or a replacement pool than the term "psychoneurosis."

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## QUANTITATIVE SEROLOGIC TESTS FOR SYPHILIS\*

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QUANTITATIVE serologic tests for syphilis have become more widely used in recent years following the introduction of intensive methods of syphilotherapy. These tests not only are useful in methods of rapid treatment but are often of considerable value in the management of various problems encountered in the diagnosis of syphilis.<sup>1,2</sup> It is the purpose of this report to discuss the indications for quantitative serologic testing and to illustrate how these tests, when used judiciously, may aid greatly in the recognition of certain manifestations occurring in syphilitic infection.

The quantitative titer of syphilitic serum may be determined by several methods. The smallest amount of antigen required for a positive reaction can be measured, the least amount of complement necessary to produce fixation can be determined or, finally, the serum can be diluted until it ceases to give a positive reaction.<sup>3</sup> The last-named technic is the one most widely used and is the method employed in our laboratory. The serologic reaction is performed with serial dilutions of serum, the reagin titer being the highest dilution of serum giving a positive result. Thus, if a serum is positive up to 1:50 dilution but negative in a 1:60 dilution, it is

said to have a titer of 50. In our patients, the quantitative Kahn test is routinely employed with serial serum dilutions of 1:5, 1:10, 1:20, 1:30 and so on. The titer is recorded in Kahn units, obtained by multiplying the maximal dilution of the serum giving a positive reaction by four. A quantitative titer below 4 units is recorded when the serum shows partial flocculation in the undiluted state and is negative when diluted.<sup>4</sup> Since the sensitivity of the test is known to vary each day,<sup>5</sup> a difference of positivity of one to two dilutions is usually not significant. Thus, change from 40 to 80 Kahn units must be interpreted with caution.

#### PRIMARY SYPHILIS

In our clinic, quantitative serologic tests are taken routinely on all patients with early syphilis, but these have proved to be of the greatest value in the cases with negative dark-field lesions. A marked rise in titer provides a simple method of identifying many such lesions as primary syphilis.<sup>6</sup> A simple positive reaction in the presence of a chancrelike lesion in which no spirochetes can be found is construed by most physicians as indicative of primary syphilis. Such a reaction is, however, compatible with the diagnosis of a latent syphilitic infection and a coexisting nonsyphilitic lesion, or it may indicate a biologic false positive reaction caused by chancroidal or lymphogranulomatous infection. The

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following case illustrates the value of an increase in titer in the diagnosis of primary syphilis.

CASE 1. L. C. H., a 25-year-old Negro, came to the clinic with a penile ulcer of 5 weeks' duration. He denied previous lesions or syphilitic treatment, and the results of previous serologic tests were not available. Physical examination was negative except for the genital lesion, which was a shallow ulceration on the glans penis 1 cm. in diameter, with a clean base and sharp edges. It appeared to be healing spontaneously. Repeated dark-field examinations revealed no spirochetes, and the Frei and Ducrey tests were negative. The quantitative Kahn test, however, showed 120 Kahn units, and within 10 days the titer rose to 600 units. This sharp rise in reagin titer indicated that the syphilitic infection had been very recently acquired.<sup>6</sup> A diagnosis of primary syphilis was therefore made, and treatment was instituted.

Although the ulcer in this case was suspected of being a chancre, this could not be proved until quantitative tests were done. When a chancre is of five weeks' duration or more, as in the above case, *Treponema pallidum* may not be found in more than 50 per cent of the cases,<sup>7</sup> and quantitative serologic tests become of diagnostic importance.

A sharply rising reagin titer is usually found in very recently acquired syphilis, a stationary titer indicates a syphilitic infection of some duration, and a falling titer without treatment usually represents a false positive reaction.<sup>6,8</sup> A considerable proportion of lymphogranulomatous and chancroidal infections have been shown to give false positive reactions for syphilis. Such reactions, which are usually of low titer, may persist for several weeks, and mistaken diagnoses of primary syphilis may easily be made in these cases.<sup>9</sup> We ourselves have on several occasions observed this phenomenon, and have become impressed with the importance of quantitative serologic tests in the presence of genital lesions that are dark-field negative.

#### CONGENITAL SYPHILIS

Titered reagin determinations in children born of syphilitic mothers have now become recognized procedures in the diagnosis of congenital syphilis. Since maternal reagin is often transmitted to the child by way of the placenta, serologic tests at birth are of little value. Approximately 15 per cent of positive cord tests revert to negative,<sup>10</sup> and about the same number of negative tests become positive when repeated later in infancy. For this reason, a child born of syphilitic parents should have quantitative tests at regular intervals to determine the disappearance of the maternal reagin or the gradual appearance of his own antibodies. In addition to this method of serial testing for the diagnosis of congenital syphilis, comparative studies of the reagin titer of mother and child may also be of diagnostic value. Almost invariably, the transmitted reagin in the child is equal to or less than that in the mother.<sup>11,12</sup> Hence, a reagin titer in the infant well above that found in the mother should be evidence of syphilis in the child. The following case is illustrative.

CASE 2. W. C., a 2-month-old Negro, was seen in the Pediatric Syphilis Clinic in February, 1944, with the complaint of peeling of the skin of the hands and feet. On examination he appeared poorly nourished and fretful. There was a desquamation of the skin of the palms and soles, a pseudoparalysis of the legs and enlargement of the spleen and liver. The mother had had eighteen injections of Mapharsen during the last 2 months of pregnancy and had delivered premature twins, both of whom appeared normal at birth. Cord serologic tests were not done.

On admission the Kahn test of the patient was positive, whereas that of the other twin was negative. During the following week quantitative tests on the family revealed that the patient had 1120 Kahn units and the mother 40 Kahn units, whereas the other twin continued to be negative. Roentgenograms showed extensive destruction and pathologic fractures of the metaphyses of the long bones, with slight periosteal reaction. The long bones of the other twin appeared entirely normal by x-ray.

Following three injections of bismuth, the patient improved remarkably, with a gain in weight and disappearance of the desquamation and pseudoparalysis. Five months later the Kahn test was 360 units in the patient and still negative in the twin.

Because of the rarity of congenital syphilis occurring in only one of twins, the possibility of transmitted reagin from the mother to the apparently infected child had to be excluded in this case. Sufficient evidence for the diagnosis of congenital syphilis was provided by the characteristic roentgenographic findings in the long bones and the reagin titer in the child, which was many times that of the mother. As noted above, however, a quantitative titer in a child less than that of its mother does not exclude the possibility of the child's having congenital syphilis.

Comparative reagin determinations in mother and child may offer an immediate method for the diagnosis of congenital syphilis. Before this method can be depended on, however, further determinations of mother and infant reagin titers are needed to confirm the observation that the transmitted maternal reagin is always less than that of the mother herself.

#### RELAPSING SYPHILIS

Just as in the initial syphilitic infection, there is frequently a rise of reagin titer in early relapsing syphilis. The clinical recognition of infectious relapse is often difficult, for the recurring syphilide frequently appears as a solitary atypical skin or mucosal lesion rather than the florid eruption of the original infection. In such cases quantitative serologic testing may offer considerable aid in making the correct diagnosis. This is particularly true when patients have never had serologic reversal and have had what could ordinarily be considered adequate syphilitic treatment. The following case is illustrative.

CASE 3. M. H. H., a 19-year-old girl, was known to have had syphilis since September, 1942, when she was found to have secondary lesions. Immediately following the diagnosis, she had received treatment without interruption and had taken a total of sixty-six injections of nearsphenamine, twenty-three of Mapharsen and six of bismuth. Because the serologic tests had never returned to negative, she was referred to the clinic for consultation.

The physical examination was entirely negative, and no evidence of syphilis was found. Blood taken on May 24, 1944, showed 20 Kahn units. The spinal fluid was normal, with no cells, negative Wassermann, Kahn and mastic reactions and 23 mg. of protein per 100 cc. Since the patient had had sufficient arsenical therapy, she was considered to be seroresistant and no further treatment was advised.

One month later the patient returned with erythematous annular lesions of the legs and erosions in the mouth. Spirochetes resembling *T. pallidum* were found in the dark-field preparation of the oral mucosa. The Kahn titer was found to have risen to 120 units, where it remained, and biopsy of the skin lesion was histologically consistent with secondary syphilis. A diagnosis of early infectious relapse was made, and phenarsine hydrochloride was given. With the first injection the mucous patches healed completely and the skin lesions regressed markedly.

In this case the clinical appearance of the skin eruption closely resembled erythema multiforme. The finding of spirochetes resembling *T. pallidum* could not be considered diagnostic, since they were from the mouth and there were no satellite nodes large enough to aspirate. The diagnosis of a mucocutaneous relapse was therefore based on the rise of reagin titer and the histologic appearance of the skin biopsy.

In using quantitative tests as an aid in the diagnosis of relapsing syphilis, it must be remembered that early cutaneous relapse is frequently, but not always, associated with a rise in titer of serum reagin. Some cases of infectious relapse show even a negative serologic reaction.<sup>12</sup> Late gummatous lesions, isolated ocular relapse and neurorelapse may show no changes in serum titer.

One of the frequent problems encountered is that of a patient who has had considerable treatment for syphilis and has finally reversed his serologic reaction, but some time later returns without clinical symptoms but with a positive reaction. The physician usually considers this condition a relapse or reinfection and reinstitutes treatment. In most cases, particularly in late syphilis, a quantitative test reveals an extremely low titer, which remains the same on repeated testing. This small amount of reagin may have been missed because of daily variations in the sensitivity of the tests in the laboratory,<sup>5</sup> thus explaining the previously negative serologic reaction. In these cases what appears to be a serologic relapse is shown by quantitative tests to be seroresistance.<sup>3,12</sup>

#### BIOLOGIC FALSE POSITIVE REACTIONS

The recognition of biologic false positive reactions is often extremely difficult, but one of the simplest aids in their detection is the use of quantitative serologic tests. A rapidly falling titer in the absence of therapy is evidence of the presence of nonsyphilitic reagin.<sup>8</sup> Even if the serologic reaction does not become completely negative; a decrease of titer or other bizarre behavior should arouse suspicion, and the other recommended procedures<sup>8</sup> for the detection of false positive reactions can then be applied. The following case is of interest in this

respect, for the quantitative test was the first clue to the elimination of syphilis in the diagnosis.

CASE 4. M.H., a 14-month-old Negress, was admitted to the Pediatric Ward on April 11, 1944, with paralysis of the right eye. She had apparently been well up to 3 days before admission, when the right eye was noticed to be turned in. There were no other symptoms, and the patient otherwise seemed to be in perfect health. She was born of a syphilitic mother who had taken inadequate prenatal antisyphilitic treatment, but the patient was found to have persistently negative Kahn reactions at 5-month intervals.

Physical examination revealed a somewhat irritable but well-nourished child with a temperature of 100°F. The right eye was deviated internally, and no lateral motion beyond the midline could be obtained. The pupillary reflexes were normal, and the other cranial nerves seemed intact. The examination was otherwise negative, and no abnormalities of the chest could be detected, despite roentgenographic findings of a consolidation in the left upper lung. The blood Kahn reaction was doubtful on admission, but became positive several days later and remained so throughout the hospital stay. On April 21 it was 280 Kahn units, on April 27 it was 2 Kahn units, and on May 28 it was 40 Kahn units. The spinal fluid contained 6 white cells per cubic millimeter and 38 mg. of protein per 100 cc. There was a mastic reaction of 444311, a positive Kahn reaction and a negative Wassermann reaction. The spinal-fluid chloride level was 720 mg., and the sugar was 60 mg. per 100 cc. Repeated spinal-fluid examinations showed essentially the same findings, with positive Kahn and negative Wassermann reactions, at both the hospital and the state laboratory. The white-cell count on admission was 17,000, with 82 per cent polymorphonuclear leukocytes. It remained much the same during the first 2 weeks of hospitalization, but fell to 10,000 by the time of discharge. The heterophil antibody test was negative. On May 28, a specimen of serum gave negative Hinton, Mazzini, Kline, Kolmer and Eagle reactions but continued to show a positive standard Kahn reaction. The Kahn verification test showed a nonsyphilitic type of reaction, with more precipitation at cold than at warm temperatures and a higher titer with normal saline solution than with hypertonic salt solution.<sup>13</sup>

Although the tuberculin test was positive, no tubercle bacilli could be found in gastric washings or spinal fluid. The temperature varied between 99 and 100°F. during the hospital stay. The roentgenographic findings did not change, and the consolidation of the lung remained the same. The final clinical impression at the time of discharge was that the patient had a primary tuberculous infection; the etiology of the cranial nerve lesion was still undetermined. Two months later, the blood and spinal-fluid Kahn reactions were negative, but no improvement was noted in either the paralysis of the eye or the pulmonary consolidation.

This occurrence of a false positive Kahn reaction in sick children with the other serologic tests remaining negative is unusual, but has been previously described by Clifton and Heinz.<sup>14</sup>

We have been struck by the high titer occasionally found in false positive reactions in children with febrile illness, the false-positive reactions usually seen in normal adults being quite low.<sup>8</sup> A single titer, therefore, no matter how high, is of no value in excluding a biologic false positive test, and repeated quantitative tests for observation of unusual titer behavior are necessary. For the same reason, a rising titer is occasionally due to an intercurrent illness rather than an actual increase of syphilitic reagin itself.<sup>15</sup> An upward trend should be verified by repeated tests before being accepted as definitive.

#### PROZONE PHENOMENON

The prozone phenomenon is one of the yet unexplained reactions that occasionally occur in

serology. It appears in a few strongly positive serums that give negative reactions when whole serum is used but positive reactions when dilutions of the same serum are employed. Zoning is not infrequently noted in the Wassermann test, but is somewhat less frequent in flocculation tests.<sup>3</sup> Such reactions have been noted recently in both the Kline and Hinton tests.<sup>16,17</sup> The following case of zoning in the Kahn test was detected when the titer was measured quantitatively.

**CASE 5.** E. K., a 30-year-old Negress, entered the hospital on January 10, 1944, complaining of postprandial abdominal distress for the previous 3 months. Physical examination revealed no abnormalities except for evidence of weight loss and midepigastric tenderness. The Kahn reaction had been reported doubtful in December, 1943, again doubtful on January 8 and also doubtful on January 10 and 12. The patient gave no history of syphilitic infection, denied previous treatment and showed no signs of syphilis on physical examination.

Because of an unusual deformity of the greater curvature of the stomach, as revealed by fluoroscopic examination, the possibility of gastric syphilis was considered. Despite the doubtful Kahn reports, a quantitative titer was requested on January 14, and the serum was found to contain more than 640 Kahn units. After gastroscopic and further x-ray examinations, the patient was diagnosed as having latent syphilis and simple gastritis, and proper diet and antisypilitic treatment were instituted. Six months later, the Kahn titer was 20 units and the prozone phenomenon had disappeared.

On the basis of a negative history and four doubtful Kahn reactions, a diagnosis of syphilis could not be made in this case. Quantitative testing, however, revealed a prozone effect that had obscured the presence of a large amount of reagin.

The incidence of serums that show the prozone phenomenon in flocculation tests is quite low, approximately 1 per 1000.<sup>16</sup> For this reason quantitative testing of all doubtful or negative reactions is obviously a waste of time. In the rare case, however, when there is strong clinical evidence of syphilis, quantitative serologic testing is indicated.

#### DISCUSSION

As shown above, quantitative serologic tests have a distinct place in the diagnosis of primary syphilis and congenital and relapsing infections and in the detection of false positive reactions and prozone effects. In intensive methods of treatment, too, the trend of the reagin titer is important in determining the immediate results of therapy, for rapid-treatment schedules are often completed before the serologic reactions have had time to reverse themselves.

Low titers are oftenest found in late syphilis and high titers oftenest in early cases, but there is so much variation that routine quantitative reactions are of little value in differentiating early from late syphilis.<sup>18</sup> For the usual diagnostic work, therefore, the routinely used qualitative test is all that is needed, since a positive reaction, regardless of the titer, is usually diagnostic of a syphilitic infection.

Furthermore, it must be remembered that the titer of reagin is in no way related to the degree of the patient's immunity and has no bearing on the prognosis or outcome of the case.<sup>18</sup> Although one is tempted to attach more significance to a high titer, it cannot be overemphasized that a patient with a titer of 4 Kahn units may be just as heavily infected with syphilis as one with a titer of 1000 Kahn units. This fact must be constantly borne in mind, for the temptation of the physician to interpret too much from the height of the reagin titer is difficult to resist.

#### SUMMARY

Quantitative serologic tests have been found to be extremely useful in the handling of various problems encountered in syphilitic infections. Serial reagin determinations may be important in the diagnosis of primary syphilis when dark-field examinations of genital lesions are negative.

Congenital syphilis in infants may be determined by comparative reagin titers in the mother and child, as well as by repeated quantitative tests during infancy. Quantitative serologic tests may assist in the recognition of early cutaneous relapse and in the differentiation of seroresistance from serologic relapse. The tests have also been helpful in the detection of prozoning and biologic false positive reactions.

Although quantitative serologic tests are indicated only in selected cases, they are nevertheless an extremely valuable tool in the diagnosis and treatment of syphilis.

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## CHRONIC MONARTICULAR ARTHRITIS\*

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CHRONIC monarticular arthritis often presents difficulty in diagnosis. With insidious onset and gradually increasing disability, the history may be confusing and the clinical and laboratory findings indefinite. Roentgenologic and pathological examination in many cases suggests only chronic inflammation, with no clue concerning the original cause. With these patients, after diagnostic aids have been exhausted, one must sometimes wait and observe the further course of the articular inflammation to determine its etiology. Until a diagnosis is made, treatment must be symptomatic and

joint is evident, and is usually a preceding injury or an acute infection. When the cause is not apparent, laboratory aids frequently give the diagnosis. Rapid recovery is the rule, and when healing is delayed, the subsequent course of the disease usually leaves no doubt concerning the diagnosis. Evidences of previous inflammation in the joints are sometimes found when there are no complaints and no evidence of disability.

The location of the disease, the duration of symptoms, the clinical impression, the course and the final diagnoses in the 14 cases of chronic mon-

TABLE 1. Summary of Data in Cases of Chronic Monarticular Arthritis.

CASE No.	AGE yr.	SEX	JOINT INVOLVED	DURATION OF SYMPTOMS	PRESUMPTIVE DIAGNOSIS	COURSE	TIME FOLLOWED yr.	FINAL DIAGNOSIS
1	6	M	Right knee	12 mo.	Rheumatoid arthritis	Increasing disability	5	Tuberculosis
2	9	F	Left hip	18 mo.	Tuberculosis	Recovery	5	Chronic sprain
3	11	M	Right knee	6 mo.	Tuberculosis	Other joints involved	4	Rheumatoid arthritis
4	14	M	Left knee	6 yr.	Tuberculosis	Increasing disability	3	Tuberculosis
5	16	F	Left knee	8 yr.	Tuberculosis	Other joints involved	4	Rheumatoid arthritis
6	18	F	Left hip	6 mo.	Acute infection	Eventual ankylosis	3	Acute infectious arthritis
7	19	F	Left ankle	18 mo.	Tuberculosis	Increasing disability	2	Tuberculosis
8	22	F	Right shoulder	6 mo.	Rheumatoid arthritis	Rapid recovery	6	Hysteria
9	31	F	Right knee	6 mo.	Acute infection	Improvement	3	Gonococcal arthritis
10	34	F	Left knee	10 mo.	Acute infection	Ankylosis	4	Acute infectious arthritis
11	37	M	Left knee	7 mo.	Tuberculosis	Recovery	7	Rheumatoid arthritis
12	42	M	Left hip	8 mo.	Tuberculosis	Died	1	Sarcoma
13	46	F	Right elbow	15 mo.	Rheumatoid arthritis	Slow progression	2	Tuberculosis
14	61	F	Right knee	6 mo.	Osteoarthritis	Slow progression	2	Tuberculosis

should be directed to the relief of symptoms and the prevention of further disability.

Fortunately, chronic inflammation in only one joint is not frequent, and this type of disease in which a diagnosis cannot be made for a prolonged period is rarer still. I have for the last ten years been recording the cases of chronic monarticular arthritis in which a diagnosis could be made only after prolonged observation. Six months of persistent symptoms was taken arbitrarily as the minimum time for considering the condition chronic. On the wards of the Robert B. Brigham Hospital 15 such patients have been observed among 2268 patients suffering from chronic arthritis. One of these, a girl of eleven with a chronic arthritis of the left hip of eight months' duration, has recently been admitted and has been under observation for only a short time. No diagnosis has yet been made, and this case is not included in the tables or in the further discussion.

Acute monarticular arthritis is relatively frequent. In most cases the cause of the inflammation in the

articular arthritis are given in Table 1. Early impressions given in our own and many neighboring clinics were often subsequently found to be wrong. The two diseases that offered the greatest difficulty in differentiation were rheumatoid arthritis and articular tuberculosis. In the average case of rheumatoid arthritis there is a gradual onset, with progression of the inflammatory process from joint to joint, followed by gradual subsidence of the inflammation, leaving varying amounts of deformity in the involved joints. When there is great variation from this clinical course, difficulties arise in making a diagnosis. In tuberculosis there is usually a mild inflammation in one joint, slowly increasing in severity concomitant with a decline in the general health. In both diseases there is often a secondary anemia, an elevated sedimentation rate and evidence in x-ray films of swelling of the soft tissues, followed by osseous atrophy. Aspiration and study of articular fluid and even biopsy may yield inconclusive results until the disease is well advanced. There is no characteristic microscopic appearance in rheumatoid arthritis. If tubercles are found, one can be relatively certain of the presence of tuberculosis. Bacteria recovered from synovial fluid are

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also conclusively pathognomonic. Failing these, if the course of the disease follows no definite pattern, one is often uncertain of the diagnosis.

In a number of these patients punch biopsies were performed to make a diagnosis or to estimate the progression of the process in the joint. This procedure was done with a No. 12-gauge tri-flanged needle with a stylet, which was removed when the desired depth in the tissues was reached. A small core of tissue was then obtained by twisting the needle and applying suction through an attached syringe. The small masses of tissue removed in this manner showed either normal tissue or chronic inflammation. The tissues were identified with

fection, 1 was a slowly growing sarcoma, 1 was diagnosed hysteria, and 1 was a chronic sprain.

The diagnostic procedures employed in attempting to arrive at a diagnosis are given in Table 2. All these patients were questioned and examined both by the house officers and by the visiting staff. There was a history of slow evolution of symptoms in half of them. In the others, there was a definite preceding injury in 4 and a sudden onset with fever suggesting an acute infection in 3. In the majority of cases examination of the joint showed only mild articular inflammation, with nothing to suggest the nature or the severity of the arthritis. The x-ray examinations were not characteristic, showing in

TABLE 2. Summary of Diagnostic Aids in Cases of Chronic Monarticular Arthritis.

CASE No.	HISTORY	PHYSICAL EXAMINATION	X-RAY EXAMINATION	BLOOD	OTHER TESTS	ASPIRATION	BIOPSY
1	Slow onset	Swollen and warm joint	Bony atrophy	Moderate leukocytosis	Tuberculin positive	Fluid negative for tuberculosis	No record
2	Patient struck by wagon	Pain and muscular spasm	Haziness of joint	Normal	All negative	No record	No record
3	Slow onset; father had tuberculosis.	Slight swelling of joint	Bony atrophy	Normal	Sedimentation rate 52 mm.	Fluid negative for tuberculosis	No record
4	Patient struck while playing	Moderate swelling of joint	Haziness of joint	Moderate leukocytosis	Tuberculin plus; sedimentation rate 65 mm.	Fluid positive for tuberculosis	No record
5	Patient fell off sled	Pain and limitation of motion	Slight bony atrophy	Mild anemia	Sedimentation rate 48 mm.	No fluid	No record
6	Followed tonsillitis	Stiff joint	Beginning ankylosis	Normal	All negative	No record	No record
7	Sprained ankle-	Swollen and painful joint	Bony necrosis (sequestrums)	Normal	Tuberculin plus	No record	No record
8	Gradual onset	Slight limitation and pain on motion	Negative	Moderate leukocytosis	All negative	No record	No record
9	Sudden onset; fever.	Flexion deformity and painful tender joint	Destruction of cartilage	Slight leukocytosis	Gonococcal fixation plus; sedimentation rate 89 mm.	No fluid	No record
10	Fever	Stiff joint	Ankylosis of joint	Normal	All negative	No record	Chronic inflammation
11	Gradual onset	Flexion deformity and moderate swelling of joint	Periarticular swelling	Normal	Sedimentation rate 57 mm.	No fluid	No record
12	Slow onset	Flexion deformity and muscular spasm of joint	Bony atrophy	Mild anemia	Tuberculin plus; sedimentation rate 30 mm.	No fluid	Sarcoma
13	Gradual onset	Swelling and stiffness of joint	Bony atrophy	Mild anemia	Tuberculin plus	Fluid positive for tuberculosis	No record
14	Slow onset	Flexion deformity and swollen joint	Bony necrosis	Normal	Tuberculin plus; sedimentation rate 94 mm.	Fluid positive for tuberculosis	No record

difficulty, and rarely could an opinion be given of the nature and severity of the inflammation in the joints. These attempts were soon discontinued. They demonstrated that satisfactory biopsies could be obtained only by adequate inspection of the articular cavity.

In this series, the duration of symptoms ranged from six months to eight years. The ages varied greatly, but the majority of the patients were children or young adults. The lower extremity was involved in most cases, a distribution that is observed in most injuries and infections involving the limbs. The knee joint was affected in 8 cases, the hip in 3, and the ankle, shoulder and elbow in 1 each. Of these 14 cases, only 2 proved to be rheumatoid arthritis, 1 was probably rheumatoid arthritis, 5 eventually were found to be tuberculosis, 2 were acute infectious arthritis, 1 was a gonococcal in-

most cases only the changes that accompany decreased function of a limb. The blood picture was usually normal. In 8 cases, the sedimentation rate (Westergren) was moderately elevated; in 3 it was normal, and in 3 it was not done since these patients were seen before the sedimentation test came into general use. The tuberculin test was positive in 6 cases. In 5 of these, the arthritis was found to be caused by tuberculosis. A strongly positive tuberculin test, although in no sense diagnostic, suggests that the inflammation is a tuberculous infection. The Wassermann reaction was negative in all these patients. The gonococcal fixation test was carried out in 6 cases; it was negative in 5 and positive in 1. It is generally reported to be positive in at least 80 per cent of cases when gonorrheal arthritis is present. Aspirations of joints gave indefinite results in 6 cases, and in 3 it showed tuberculous in-



fection. There is no record of aspiration in the other cases. Surgical biopsy was performed only when the severity of the disability suggested that this procedure might greatly modify the treatment.

### CASE REPORTS

**CASE 1.** A 6-year-old boy 1 year before admission fell upon his right knee which gradually became more swollen and limited in motion. It was treated in an outpatient clinic with support, a sprain being the presumptive diagnosis.

Examination at admission showed a swollen, hot knee, mildly tender on pressure. There was a 30° flexion deformity. There was a slight afternoon temperature. X-ray examination of the chest was negative. The blood showed a slight anemia, with a white-cell count of 14,600. A Wassermann test was negative and a tuberculin test positive. Aspiration of the knee showed clear fluid with a few polymorphonuclear cells. Injection of the joint fluid into a guinea pig failed to give evidence of tuberculosis. X-ray examination of the knee showed swelling of the soft tissues and slight osseous atrophy. The symptoms subsided somewhat and the patient was permitted to walk with a knee support. He was discharged to a state hospital.

Four years later he was walking without a limp, there were no complaints, and the right leg was 2.5 cm. longer than the left. The unproved diagnosis at the state hospital was healed tuberculosis.

**CASE 2.** A 9-year-old schoolgirl was struck by a wagon on the left leg 1½ years before admission, the injury being followed by pain and limitation of motion in the left hip. The mother had died of tuberculosis but had had no contact with the patient after she was two weeks old.

Examination showed moderate limitation of flexion and abduction of the left hip. X-ray examination showed haziness of the hip joints, the chest being negative. The blood showed nothing abnormal. Tuberculin and Wassermann tests were negative. Under bed rest the symptoms subsided entirely in 3 months.

The patient has remained well for 5 years since discharge. The probable diagnosis was chronic sprain of the left hip.

**CASE 3.** An 11-year-old schoolboy complained of pain and swelling of the right knee of 6 months' duration. There was no history of injury. His father had a healed tuberculous lesion of the right ankle.

Examination showed moderate swelling and fluid in the right knee. There was a 20° flexion deformity. On x-ray examination there was swelling of the soft tissues. X-ray films of the chest were negative. The blood showed nothing abnormal. Wassermann and tuberculin tests were negative. The sedimentation rate was 52 mm. Injection of aspirated joint fluid into a guinea pig failed to give evidence of tuberculosis. The patient was given bed rest and a plaster cast for the right leg. The symptoms entirely subsided in 4 months. A tonsillectomy was then performed and he was discharged home.

He remained well for 4 years, when he began to have pain and stiffness in the right hip and low in the back. He was readmitted to the hospital. X-ray examination showed advanced arthritis of the spine, and the disease progressed to ankylosis of the entire spine and both hips. A severe glomerular nephritis developed. The patient is now completely helpless in a rest home. The final diagnosis was rheumatoid arthritis.

**CASE 4.** A 14-year-old boy was struck in play on the right knee 5 years before admission, and was treated at intervals in a hospital clinic. The symptoms partially subsided and he continued going to school, but the knee remained swollen and limited in motion. Four months before admission the symptoms became worse.

Examination showed marked swelling and limitation of motion. The white-cell count was 13,600, with 44 per cent lymphocytes. The sedimentation rate was 65 mm. Gonococcal-fixation and Wassermann reactions were negative. A tuberculin test was positive. X-ray examination of the knee showed narrowing of the joint space and thickening of the

soft tissues. The chest showed thickening about the roots of the lungs but no definite evidence of tuberculosis. Injection of fluid aspirated from the knee produced tuberculosis in a guinea pig. The boy was transferred to a sanatorium for the treatment of tuberculosis.

The diagnosis was tuberculosis of the knee.

**CASE 5.** A 16-year-old schoolgirl entered the hospital complaining of pain and swelling of the left knee of 8 years' duration, coming on after a fall from a sled. There was intermittent swelling but no pain. Tuberculosis was suspected in another clinic, although x-ray examination showed only slight bony atrophy. Aspiration of the joint was negative. Symptoms subsided completely after 18 months in a convalescent home. The patient remained well for 6 years but 4 months preceding admission she began to have swelling, pain and limitation of motion in the left knee, right ankle and right wrist.

On admission there was no increased heat or tenderness in the joints or other noteworthy findings. Examination of the blood showed a slight anemia, with a white-cell count of 7800. Wassermann and tuberculin tests were negative. The sedimentation rate was 48 mm. X-ray examination showed slight bony atrophy and periarticular swelling about the involved joints. During the stay in the hospital the hands and elbows and hips also became inflamed. The patient gradually improved and was discharged after 8 months.

She has since been followed in the outpatient clinic for 5 years. The only remaining disability is slight limitation of motion in the left hip and right elbow. The diagnosis was rheumatoid arthritis.

**CASE 6.** An 18-year-old girl entered the hospital complaining of pain and increasing stiffness of the left hip of 6 months' duration. The onset of symptoms followed an attack of tonsillitis. She was treated in a suburban hospital, where the throat infection subsided and the symptoms in the hip decreased.

Examination on admission showed moderate atrophy of the musculature of the left hip joint but was otherwise negative. The blood showed no abnormal findings. Wassermann and tuberculin tests were negative. A vaginal smear showed no gonococci. X-ray examination showed almost complete loss of cartilage at the left hip joint, with bony atrophy; there was no definite osseous destruction. The leg was made comfortable in a plaster cast with the hip held in slight flexion and abduction. All motion at the hip was soon lost, and x-ray films showed beginning bony ankylosis.

The patient was subsequently followed for 3 years. She remained well during this period, but the left leg was ankylosed. The diagnosis was acute infectious arthritis followed by ankylosis.

**CASE 7.** A 19-year-old Italian candy maker was admitted complaining of pain and swelling of the left ankle coming on after a sprain of the ankle 2 years before. There was a definite limp, but pain was not severe.

Examination showed extensive swelling on both sides of the ankle, with fluctuation on the outer side. The temperature was normal. Examination of the blood showed no definite abnormality. A Wassermann test was negative, and a tuberculin test was positive. The x-ray films showed necrosis of the os calcis, with several small sequestrums. Biopsy demonstrated tuberculosis.

The patient gradually improved in a convalescent hospital. There she developed a psychosis and has since been confined in a state mental hospital. The final diagnosis was tuberculosis of the ankle.

**CASE 8.** A 22-year-old waitress complained of pain and stiffness of the right shoulder of 6 months' duration, which appeared after a severe throat infection. The condition had remained practically unchanged until admission.

Examination showed moderate limitation of motion and slight pain on motion of the right shoulder. The white-cell count was 15,000. The sedimentation rate was 17 mm. Wassermann and gonococcal-fixation tests were negative. X-ray examination of the shoulder showed no abnormality. A psychiatric examination revealed an unstable personality

with difficulty in adjustment and frequent changes of jobs. A 3-month pregnancy had been terminated by abortion shortly before the onset of symptoms. The symptoms quickly subsided in the hospital. A better environment and more congenial employment was provided by the Social Service Department.

The patient has been followed for 6 years and has had no further trouble in the shoulder. The final diagnosis was hysteria.

**CASE 9.** A 31-year-old schoolteacher had pain and swelling of the right knee of 6 months' duration. There was no history of injury. A cast was applied to the knee for the relief of pain at a suburban hospital, but was soon removed. The condition remained practically unchanged.

On examination there was a 30° flexion deformity of the knee, which was tender and showed increased heat. The white-cell count was 11,350. The sedimentation rate was 89 mm. The gonococcal-fixation test was positive. Wassermann and tuberculin tests were negative. X-ray examination showed periarticular swelling with beginning destruction of the articular surfaces. A cervical smear showed no gonococci. No fluid was obtained on aspiration. Under rest and physiotherapy the symptoms slowly subsided.

After 4 months there was improved motion in the knee, which has remained unchanged for 8 years. The final diagnosis was probably healed gonococcal arthritis.

**CASE 10.** A 34-year-old housemaid had pain and tenderness, followed by inability to move the left knee, of 10 months' duration. She had had a fever for the first 2 weeks of her illness.

Examination showed slight swelling and tenderness over the left knee. There was no motion in the joint. Wassermann and tuberculin tests were negative. The blood examination showed no abnormal findings. X-ray films showed destruction of the articular surface and beginning ankylosis. There was no evidence of gonococcal infection. The symptoms subsided entirely as ankylosis occurred.

The patient has remained symptomless for 6 years. An operation performed later to secure motion showed chronic inflammation in the joint. The diagnosis was acute infectious arthritis with ankylosis.

**CASE 11.** A 37-year-old farmer entered the hospital for the relief of pain and limitation of motion in the left knee of 7 months' duration. The onset was gradual, and there was a history of a sprain of the left thigh in lifting a heavy object shortly before.

Examination showed moderate swelling of the knee with slight flexion deformity but no tenderness or increased heat. The physical examination was otherwise negative. The blood was normal. Wassermann, gonococcal-fixation and tuberculin tests were negative. The sedimentation rate was 57 mm. A prostatic smear was negative. Aspiration of the joint showed nothing abnormal. X-ray films of the chest were negative. X-ray examination of the knee showed swelling of the periarticular tissues only. With bed rest and physiotherapy there was a rapid regression of symptoms in 3 months. Chronically infected tonsils were then removed without incident.

The patient has remained completely well for 9 years since discharge. It was the impression of the staff that this was a healed rheumatoid arthritis of the knee associated with a chronic upper respiratory infection, although the possibility of a chronic sprain of the knee could not be excluded.

**CASE 12.** A 42-year-old storekeeper was admitted complaining of pain and stiffness in the left hip of 8 months' duration. He had lost 10 pounds in weight during the previous 2 months.

Examination showed muscular atrophy, muscular spasm and a 20° flexion deformity at the right hip. There were no other significant findings. Examination of the blood showed a mild hypochromic anemia. The sedimentation rate was 30 mm., and gonococcal-fixation tests were negative. A tuberculin test was positive. X-ray films of the chest showed nothing remarkable. The hip showed a small area of calcification in the body of the ischium, with increased density in the acetabulum. According to the roentgenologist, this was suggestive of tuberculosis. Aspiration of the joint gave no fluid. The serum calcium, phosphorus and phos-

phatase levels were within normal limits. The patient had increasing pain, which was not relieved by traction or a plaster spica.

He was transferred to a tuberculosis sanatorium in his home state, where continuance of severe pain eventually led to an operation on the hip. Examination of tissue from the ischium showed a chondrosarcoma. The patient died 2 months later. The diagnosis was sarcoma of the left ischium.

**CASE 13.** A 46-year-old housewife had increasing soreness and limitation of motion in the right elbow of 5 years' duration. There was no related history of injury or infection. Her general health had remained good. X-ray examination by the family physician 1 year previous to admission showed bony atrophy about the elbow. A diagnosis of rheumatoid arthritis was made and physiotherapy was given, without relief.

Examination showed a 90° flexion deformity at the right elbow and 5° of painful motion. The elbow was swollen to about twice the normal size and was slightly tender, but showed no increased heat. General examination showed no other significant findings. X-ray examination of the chest was negative. The elbow showed bony atrophy and narrowing of the joint space. The sedimentation rate was 18 mm. Wassermann and gonococcal-fixation tests were negative. The tuberculin test was positive. Fluid aspirated from the joint and injected into a guinea pig showed tuberculosis.

There has been a gradual improvement in the elbow following immobilization and heliotherapy. The diagnosis was tuberculosis of the elbow.

**CASE 14.** A 61-year-old housewife entered the hospital complaining of pain and stiffness in the right knee of 6 years' duration.

Examination showed moderate swelling and limitation of complete extension in the right knee. It was not tender, and there was no increased heat. The fingers showed Heberden's nodes. X-ray examination of the chest revealed an old tuberculous lesion in the right upper lobe. That of the knee showed narrowing of the joint space, an area of destruction over the femoral condyle and extensive osteoarthritis. The blood was normal. The Wassermann reaction was negative. The sedimentation rate was 94 mm. The tuberculin reaction was positive. The symptoms subsided with physiotherapy and a support for the knee.

The patient remained well for 3 years, when she returned presenting a draining sinus over the knee. Fluid aspirated from the joint and injected into a guinea pig resulted in tuberculous infection. The patient has been at a state tuberculosis sanatorium for the last 2 years. The diagnosis was tuberculosis of the knee.

The experience encountered in these cases has made us more cautious in accepting an immediate diagnosis in any patient with chronic monarticular arthritis. There are no signs or clinical findings that are in themselves pathognomonic of rheumatoid arthritis. If healing occurs gradually, even long observation may not solve the question; likewise, it is difficult to demonstrate a histologic picture in articular tissue that is sufficiently characteristic to establish the diagnosis. In the presence of unrelated infection, chronic trauma — for example, sprain — that has not healed because of inadequate treatment may easily simulate rheumatoid arthritis. Rheumatoid arthritis, as these patients show, rarely remains monarticular, but tends to revert to the usual picture after a few years. Undoubtedly, if the patient remains well, monarticular rheumatoid arthritis may heal and not recur, but this is a rare occurrence. Whether in certain of the patients tuberculosis was superimposed on an already existing rheumatoid or osteoarthritis or whether a quiescent infection was activated by injury or irritation, cannot be decided at the present time. Slow-

growing tumors adjacent to joints may counterfeit chronic arthritis until the further development of the tumor establishes the diagnosis. Hysteria simulating joint symptoms is rare.

In atypical chronic arthritis, particularly when it is monarticular, the diagnosis must be made with caution; in rare cases it cannot be made definitely, long observation helping only to confirm the presumptive diagnosis. Symptomatic treatment is indicated until the diagnosis is established, when other measures directed against the cause of the inflammation can be added. Deformity is prevented by traction, a plaster cast or other appropriate apparatus. When a definite diagnosis has not been made, attempts should be made to promote strength and motion in the joint as the symptoms subside. A number of other therapeutic procedures are useless or positively harmful in certain diseases, and

these should be avoided until a definite diagnosis has been established.

#### CONCLUSIONS

Chronic monarticular arthritis in which a diagnosis cannot be easily made is infrequent. Often the cause of the inflammation can only be determined by observing the further course of the disease. During this time, treatment must be symptomatic and must be directed to preserving articular function so far as possible. Any procedure that may be harmful should be avoided. No definitive treatment — for example, surgery — should be carried out until the diagnosis has been established. Chronic monarticular arthritis is rarely due to rheumatoid arthritis.

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## THE EFFECT OF PENICILLIN ON INOCULATION MALARIA\*

## A Negative Report

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BOSTON

UNDER a well-organized national program, clinical and laboratory data showing the therapeutic effectiveness of penicillin in many disease conditions are rapidly accumulating. Re-

laxing tertian malaria in many of the returning troops is proving a definite problem. The chief concern is about the best method for the active treatment of these relapses and about the possibility

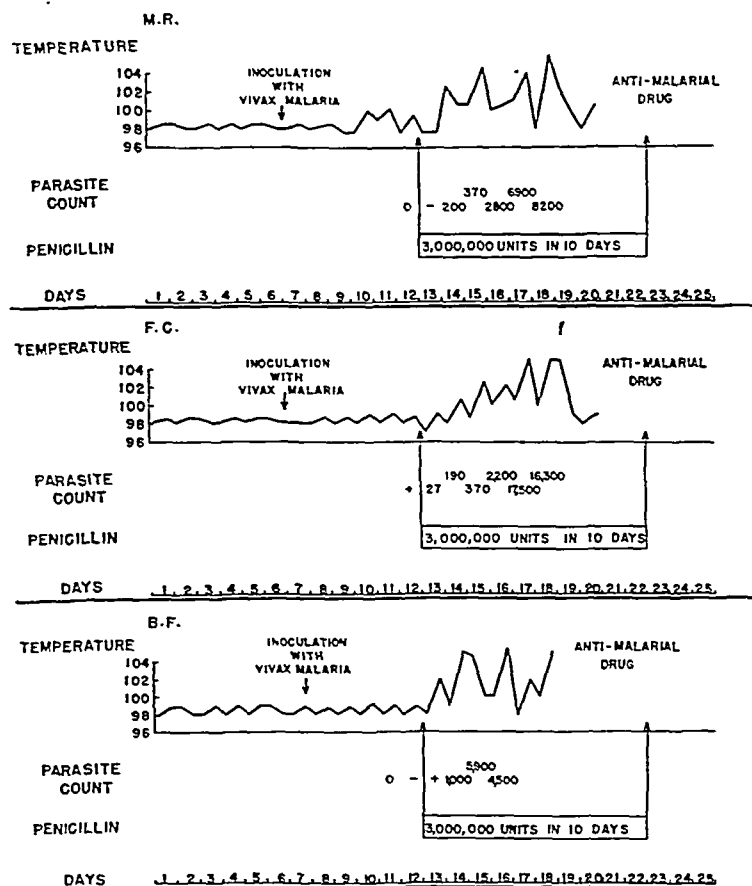


FIGURE 1. Charts of Case Receiving Penicillin after the Development of Parasitemia and Fever.

*It should be observed that parasites increase and fever occurred in the usual sequence. The malarial course was then altered by the administration of an anti-malarial drug under investigation.*

cently penicillin has been made available for more widespread civilian use in certain specified infections. There are few factual data available concerning its efficacy in malaria.

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The work described in this paper was performed with penicillin supplied by the Office of Scientific Research and Development. It was done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts General Hospital.

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that such malarial infestations will form a reservoir for a marked increase in cases among the general population. It is natural, therefore, for questions concerning the effect of penicillin on malaria to arise. It is hoped that this negative report will serve to answer some of these questions.

As a research grant from the Office of Scientific Research and Development for the treatment of neurosyphilis, penicillin was issued to the Boston

Psychopathic Hospital in February, 1944. Simultaneously, a unit for the study of antimalarial drugs was established at this hospital under O.S.R.D. Contract No. OEMcmr-419. Under this double investigative program 28 patients with neurosyphilis have been treated by the combined use of penicillin and benign tertian malaria. In 15 of these cases the two forms of therapy overlapped in such a way as

beginning of fever (101.6°F., rectal), the temperature was taken every hour. Parasite counts, by a slight modification of Earle's method, were performed daily.

### RESULTS

The 15 cases in which penicillin and fever therapy were given together are divided into two groups

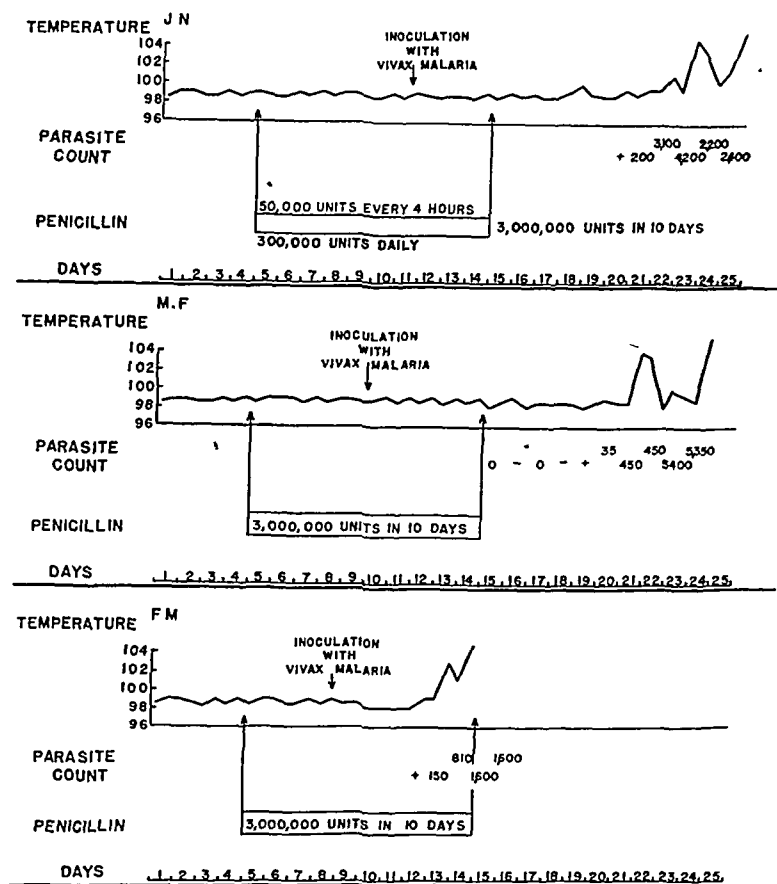


FIGURE 2. Charts of Cases Receiving Penicillin Several Days before the Inoculation of Malaria.

It should be noted that, after a variable incubation period, increasing numbers of parasites and paroxysms of fever appeared.

to make it possible to draw conclusions concerning the effect of penicillin on this form of malaria. The clinical charts of some of these cases form the basis of this report.

### METHOD AND MATERIAL

Penicillin was administered in all cases intramuscularly, 50,000 Oxford units being given every four hours for ten days, a total of 3,000,000 units. Therapeutic malaria was induced by *Plasmodium vivax* (McCoy strain) in all cases. A calculated standard inoculum of 500,000 parasites, taken from an active case, was injected intravenously. The cases were selected, so far as possible, to avoid natural immunity. After inoculation, each patient's temperature was taken rectally every four hours. At the

In Group 1 (6 cases), penicillin was administered after the development of fever and parasitemia. Figure 1 shows the clinical charts of 3 patients. Penicillin caused no reduction in fever, no significant alteration in the timing of the paroxysms and no reduction in the level of parasite counts in any of the cases. These results demonstrate that penicillin does not suppress the clinical manifestations of inoculation *P. vivax* malaria.

In Group 2 (9 cases), penicillin was started before the development of fever. These cases are subdivided into 4 cases in which penicillin was started a few days before the malarial inoculation (Fig. 2) and 5 cases in which it was started at approximately the time of the malarial inoculation (Fig. 3). The clinical charts of these cases demonstrate that

penicillin does not prevent or postpone the development of inoculation *P. vivax* malaria. This seems of special significance, since the number of parasites in the recipient is lowest at the time of inoculation, and if penicillin has any antimalarial action at all, it should have been shown by this experiment.

## DISCUSSION

Inoculation malária differs in certain respects from natural-occurring, mosquito-induced malaria.

In this study only the McCoy strain of *P. vivax* was used. Accordingly, it is not possible to draw definite conclusions concerning penicillin in *P. malariae* and *P. falciparum* infections. If one reasons by analogy to known antimalarial drugs, however, it can be presumed that since penicillin shows no antimalarial activity against *P. vivax* infections, it will have none against the other types.

In a review of penicillin therapy in the United States Army published in December, 1943, Lyons\*

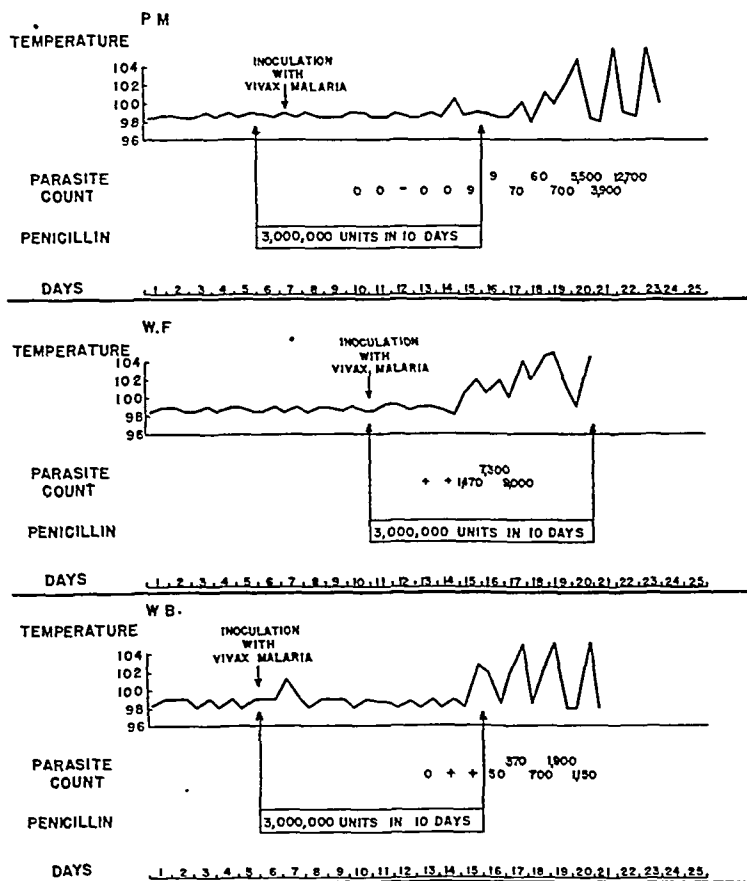


FIGURE 3. *Charts of Cases Receiving Penicillin on or about the Same Day as the Malarial Inoculation.*

It should be observed that, after a variable incubation period, parasites appeared and increased in number, and paroxysms of fever occurred in the characteristic manner.

It is produced by the transfer of trophozoites from patient to patient. The incubation period is usually shorter by a few days or a week; parasite counts as a rule do not reach quite such high levels; and, although the temperature response may be just as severe as in mosquito-induced malaria, the disease is more satisfactorily suppressed by antimalarial drugs. Cases of inoculation malaria (induced for therapeutic fever) comprise ideal subjects for the testing of drugs with antimalarial activity, for over a period of many years the disease has been well standardized and it has been clearly shown that drugs that do not suppress trophozoite-induced malaria do not suppress sporozoite-induced malaria.

states: "Malaria due to *Plasmodium vivax* is not affected by penicillin. In addition to the 4 recorded failures, 2 other patients have developed recurrent malaria under treatment." No other reference to the effect of penicillin on malaria has been found in the literature.

## SUMMARY AND CONCLUSIONS

During investigations on the use of penicillin in neurosyphilis, 28 patients received both penicillin

\*Lyons, C. Penicillin therapy of surgical infections in U. S. Army. *J. A. M. A* 123:1007-1018, 1943.

and benign tertian malaria. Fifteen of these had penicillin administered simultaneously with the malaria. Clinical charts of 9 cases are presented. These charts graphically demonstrate that penicillin does not suppress fever or the parasite count of active inoculation malaria and that when given before or at the time of the malaria inoculation it does not prevent or postpone the development of fever and parasitemia.

It is reasoned by analogy to known antimalarial drugs that since penicillin does not have an anti-malarial effect on inoculation *Plasmodium vivax*

malaria, it will not be effective in other types of malaria or in naturally acquired malaria.

Since the writing of this paper we have had further experience in the use of penicillin in therapeutic malaria. In view of the fact that penicillin is rapidly removed from the body, we have tried more frequent injections to exclude this possible loophole in the ineffectiveness of the drug. We have given 3,000,000 units in five days at the rate of 50,000 units at each intramuscular injection every two hours, day and night. This method has been used in about 20 cases without any change in the paroxysms of fever or in the parasitemia.

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**Addendum.** Through an oversight, permission to reprint the two articles "Justice and the Future of Medicine," by Wendell Berge, Esq., and "A Urologist Looks at Changing Trends in Medical Practice," by Dr. Herman L. Kretschmer, which appeared in the November 30, 1944, issue of the *Journal*, was obtained from the editor of the *Journal of Urology* but not from the copyright owner, The Williams and Wilkins Company, Baltimore. Permission has been obtained *ex post facto* and is herewith gratefully acknowledged.

# MEDICAL PROGRESS

## ORTHOPEDIC SURGERY: THE PROBLEM OF THE INTERVERTEBRAL DISK

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THE cause of the backache has for years intrigued orthopedic surgeons. Many popularized diagnoses, such as sacroiliac slip, lumbosacral strain and so forth, represent phases of progress in unraveling the mysteries of back pain. Backache associated with pain in the leg has frequently been inaccurately labeled "sciatica" by doctors and the laity alike. The recent trend is to abolish this term because it carries no accurate connotation concerning either the cause or the distribution of pain. In 1934 a new spark of interest was aroused by Mixter and Barr<sup>1</sup> when they introduced the syndrome ascribed to herniation of the nucleus pulposus. A profusion of literature attests to the popularity of this new syndrome, variously referred to as ruptured intervertebral disk, protruded disk and herniation of the disk. The purpose of this report is to give a concise notion of the factual information, as well as the controversial opinions, that exists regarding the intervertebral-disk syndrome as it is known today.

The embryologic development of the spine, with special reference to the intervertebral disk, has been studied by Ehrenhaft,<sup>2</sup> and the point he emphasizes is the avascularity that occurs in the disk after the age of twenty-five. Possibly this has a bearing on the etiology of pathologic disks. The question of trauma as the cause of rupture of the intervertebral disk remains unsettled. Hyndman, Steindler and Wolkin<sup>3</sup> are inclined to believe that even in the few patients who describe the root pain as being coincident with the back injury there has been a preceding back injury. Inman and Saunders,<sup>4</sup> in a detailed account of the anatomy of the intervertebral disk, point out the frequency of protruded disks in the region on the intervertebral foramen, where the postligamentous support between vertebral bodies is weakest. They estimate, by an analysis of force vectors resultant upon the lower lumbar disks in lifting a weight of 50 pounds, that, under average conditions, a pressure amounting to about 500 pounds is exerted. In addition, when the spine is flexed, the nucleus pulposus in the lumbar region migrates dorsally, tension is thrown on the posterior portion of the annulus, and if some rotation accompanies flexion, the annulus is further subjected to torsional stresses. These forces alone can cause herniation. If a single injury results in herniation, it presupposes a considerable tear in the tough annulus fibrosus. At operation the

posterior ligament frequently is found intact, but when incised reveals a loosened free portion of dense fibrous tissue that must be as much a part of the annulus as of the nucleus pulposus. These cases make one wonder whether some type of pre-existing degeneration is responsible for the separation of a fragment. At present there are many unanswered questions pertaining to the pathogenesis of the protruded-disk syndrome.

Young and Brailsford<sup>5</sup> carefully followed 497 patients with backache and give a numerical notion concerning the relative frequency of ruptured disks. These figures were taken from a clinic in which both soldiers and industrial workers were cared for. Of the total number, pain was localized in the back in 206 cases, was associated with referred leg pain in 204 cases and was associated with referred trunk pain in 87 cases. One hundred and three soldiers with leg pain were studied for the presence of a ruptured intervertebral disk. Of these cases, laminectomy was performed in 15; 9 cases showed definite protrusion, 2 cases had a thickened ligamentum flavum, and in 4 cases no abnormality was found. These figures tend to indicate that in all cases with referred pain in the leg approximately 10 per cent will prove to be due to ruptured disks.

The exact cause of the pain in the disk syndrome has not been clearly established. The evidence suggests direct nerve-root pressure as a major source of radiation pain in the many patients who have had relief of pain after removal of the mass. In view of the fact that many patients are not relieved of this pain following operation, one must always keep in mind other mechanisms of pain production. Such mechanisms must explain the leg pains in cases in which exploration has failed to reveal a protruded disk, as well as similar leg pains in a large group of other conditions, such as ligamentous injuries, fractured facets, hypertrophic overgrowths, impinging spinous tips, unstable lumbosacral junctions associated with various congenital anomalies, arachnoiditis, malignant neoplasm, infectious lesions, rheumatoid arthritis and sacroiliac strain.

Steindler et al.<sup>3</sup> have shown that referred pain can be completely eliminated by interrupting a reflex arc. He has traced the reflex pathways that connect the lesion to the so-called "trigger points of localized sensitivity," as well as to the referred pain in the leg. These pathways can be interrupted by an injection of novocain into the trigger point or points. From a practical standpoint he has been able to relieve pain in about one fifth of the cases

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of referred pain in which the cause was other than a protruded disk.

Intervertebral disks have been shown to contain nerve fibers.<sup>2</sup> This makes it possible for the pain to arise within the disk space, particularly when the disk is subjected to excessive pressure or when it is the seat of degenerative disease. Inman and Saunders<sup>4</sup> were struck by the clinical findings in cases of protruded disks, inasmuch as the areas complained of by the patients were quite similar, whether the protrusion was causing pressure on the fourth or fifth lumbar or first sacral nerve root. This led them to adopt a new sclerotome, rather than dermatome, distribution of referred-pain areas. The reader is urged to read the original article in order to comprehend completely this feasible conception.

The idea has many times been expressed that any backache associated with radiation pain into the thigh or leg is due to a ruptured disk. Certainly one should look carefully into the history for more distinguishing features of a ruptured intervertebral disk. Many cases with a presumably classic history of a protruded nucleus have, on exploration, revealed no findings to substantiate the diagnosis. On the other hand, explorations have revealed ruptured disks to account for local pain in the back, as well as motor and sensory disturbances, without pain in the thigh or leg. The above facts suggest that a "classic history" is nonexistent. The history should give clearly the onset, course, type and distribution of the pain, as well as associated phenomena, such as paresthesias, motor weaknesses and so forth. Statistically, however, there are no symptoms, individual or in the aggregate, that occur with great enough frequency to be considered pathognomonic. In general, the outstanding symptom is pain. This is usually recurrent in the back, with eventual radiation into the posterolateral thigh, the lateral calf and the outer side of the ankle. It is relieved only partially by changes of position, especially those in a direction of spine flexion. Aggravation usually occurs during sneezing or coughing, and is caused by sudden motions, especially those of extension. Paresthesias, when present, are described as numbness or coldness and are not stationary. Motor weaknesses occur in a small percentage of cases and, when present, are continuous. A history of trauma has been reported in from 30 to 60 per cent of cases.

No attempt has been made to separate the symptoms of a bulging unruptured disk from those of a free loose fragment or of a simple unstable disk. This may become important as we learn more about the indications for treatment. At present, so few of the fundamentals regarding the pathogenesis of symptoms are known that only by clarification of these fundamentals can one hope to be more specific.

What has been said about a lack of knowledge to explain symptoms can be applied equally well to the findings on physical examination. In general

the lumbar spine is held in flexion and a list is present. Motion of the lumbar spine is limited in all directions, but mainly in extension and lateral bending toward the side of the pain. Straight-leg raising reproduces the pain at a low level. A positive jugular-compression test, paresthesias, muscular weakness and a diminished to absent ankle or knee jerk on the affected side may or may not be present. When the last is present, it strongly suggests the presence of nerve-root pressure. With present understanding of the problem, no one point of history or no one physical finding is pathognomonic of a ruptured disk. A combination of all the facts of the history and all the physical signs should lead the examiner to look for further corroborative evidence, in order to make an accurate diagnosis.

Logically, one looks to x-ray methods for the demonstration of a space-occupying lesion in the spinal canal. Because of the failure of earlier methods, such as air myelography, to be convincing in the majority of cases, substitute methods are being tried. Lipiodol, used according to the method of Kubik,<sup>6</sup> is popular, and most of the oil can be withdrawn by an experienced person. Pantopaque, a thinner oil that maintains a good column, is gaining in popularity as a contrast medium. Substances such as Thorotrast give a less dense shadow, through which midline disks can be visualized,<sup>7</sup> but because of definite dangers, the advantages probably do not exceed the risk of its use. Spurling<sup>8</sup> has been able to localize clinically the level of the protruded disk in 60 per cent of his cases, but in the 40 per cent in which doubt existed, he resorted to the use of Pantopaque. It is well known from surgical exploration that protruded disks are found in cases in which the x-ray films were negative; conversely, protrusions are not always found in cases in which the films were positive. Horwitz<sup>9</sup> has emphasized the discrepancy between x-ray and operative findings. Degenerative disk disease, overgrowths of articular facets and the normal bulging of an overlying ligamentum flavum, by virtue of its anatomic arrangements, are potent causes of defects in the contrast column that can be mistaken for disk fragments. When the contrast medium allows good lateral visualization of the spinal canal, the above-mentioned defects are seen to lie posteriorly and can thereby be more accurately interpreted.

Before leaving the subject of x-ray diagnosis, the value of bone films should be mentioned. Scott<sup>10</sup> has reviewed in detail the radiography of facets, bony overgrowths and fractures, all of which enter into the differential diagnosis. Such films should be a routine part of every back examination.

A narrowed intervertebral space as observed in x-ray films is of no consistent diagnostic value. Vinke and White<sup>11</sup> have conclusively shown that narrowing occurs congenitally, and this condition has been observed frequently as an incidental x-ray finding during examination for symptoms other

than those referable to the spine. Ver Bruggen,<sup>12</sup> reporting the end results in 66 cases of herniated disk found narrowing of the space in only 30 per cent of the cases. Stump and Narius<sup>13</sup> reported an interesting observation in a patient with meningitis who responded to therapy but who subsequently had severe low-back pain without radiation. X-ray films revealed loss of disk space between the fourth and the fifth lumbar vertebra, without fever to indicate active infection, and the authors concluded that repeated lumbar punctures at that level had entered the interspace and had precipitated a degeneration.

From the foregoing, it is obvious that positive criteria for the diagnosis of a ruptured intervertebral disk are lacking. When the history and examination are suggestive of a protruded disk, bone x-ray films should exclude such possibilities as gross fracture, malignant neoplasm, infection or generalized bone disease. Myelography should be done to show the presence of a space-occupying lesion in the spinal canal, as well as the level or levels of the lesion. An elevated total-protein level in the spinal fluid is helpful, Ver Bruggen<sup>12</sup> having stated that good results from the removal of a ruptured disk can be anticipated in cases in which the total protein is over 40 mg. per 100 cc. The final diagnosis at times can be made only by exploratory laminectomy. This method of diagnosis should be reserved for the cases in which the severity of the pain justifies the operation.

When a diagnosis of ruptured disk has been made, the method of treatment must be selected. End-result study is the only available means of determining the effectiveness of treatment. Sufficient end results have not been reported to draw definite conclusions. Bradford<sup>14</sup> has reviewed the technical advances of operative removal, but stresses a pre-operative period of conservative treatment, as does Pilcher.<sup>15</sup> If the pain is intractable and refractory to conservative treatment, this fact in itself has been offered as evidence in favor of the diagnosis of ruptured disk, and also as an indication for operation.

Poppen's<sup>16</sup> technic for removal of the ruptured disk represents the commonly accepted type of hemilaminectomy and extradural approach. Spinal fusion has frequently been combined with the removal of the disk in cases in which there is evidence to suggest instability of the spine. No information is available to intimate the number of cases in which fusion has been done, but it is apparent that such an operation is indicated for continued disability after simple removal of a protrusion.

The final chapter either in the diagnosis or in the treatment of ruptured intervertebral disks has not yet been written. Only by a continued careful analysis of cases and by an honest appraisal of their end results can the data necessary to produce the answer to the present questions be accumulated.

264 Beacon Street

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor\**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 31051

#### PRESENTATION OF CASE

A forty-nine-year-old married woman was admitted to the hospital with a palpable mass in the upper abdomen.

The patient had been in good health until three months prior to admission, when she developed a mild ache in the midportion of the back. This was followed in a few hours by a rather diffuse, nonradiating ache in the epigastrium, accompanied by nausea. On one occasion she vomited undigested food recently eaten. There was no hematemesis, jaundice or change in bowel habits, and the stools were of normal appearance. After three days the symptoms completely disappeared. The physician whom she consulted, however, felt a mass in the epigastrium. About two months prior to entry an x-ray examination revealed an "ulcer of the small intestine." At that time the mass was thought to be smaller on palpation. She continued to feel well, with an excellent appetite, and had no recurrence of symptoms, but because of the persistent mass was finally admitted to the hospital for study.

Three years before entry she had undergone a hemorrhoidectomy, with excision of an anal fistula. Her menstrual periods had been regular until five months prior to admission, when she developed amenorrhea, interrupted only by a scanty one-day period about a month before entry.

Physical examination revealed a well-developed and well-nourished woman in no discomfort. The lungs were negative except for some decrease in tactile fremitus over the left apex. The heart was negative. A firm, smooth, nontender, nonpulsating mass was palpable in the epigastrium; it was movable and shifted with respiration. No continuity with any abdominal organ could be demonstrated.

The temperature, pulse and respirations were normal. The blood pressure was 128 systolic, 75 diastolic.

Examination of the blood showed a white-cell count of 8700, with 73 per cent neutrophils, 19 per cent lymphocytes, 7 per cent monocytes and 1 per cent eosinophils. The urine had a specific gravity of 1.020, with a + test for albumin; the sediment

\*On leave of absence.

contained a few white cells per high-power field. A stool examination was negative. A Hinton test was negative.

A gastrointestinal series revealed an esophagus that was slightly wider than normal. There was no definite evidence of varices. The stomach was rather long and large, and the lesser curvature in the region of the antrum and lower body revealed a large extrinsic pressure defect (Fig. 1). The duodenal cap and second portion of the duodenum were displaced laterally and also showed evidence of extrinsic pressure. A barium enema revealed no abnormalities. An intravenous pyelogram revealed normal kidney outlines, prompt dye excretion and normal urinary passages.

On the seventh hospital day a laparotomy was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. GEORGE W. HOLMES: Before taking up the x-ray findings in this case I should like to go over the history briefly. I think it is quite important for a radiologist to know something about the history of a patient before he attempts examination, because, unless he does, he is likely to leave out of the examination some of the most significant procedures. I shall therefore approach this case as I think a radiologist should.

The first points of importance are the age of the patient and the duration of the illness. This woman was nearly fifty and she had trouble three months prior to coming into the hospital. There is no reason to suppose that the presenting mass had been there prior to the onset of the symptoms that are described. It was a sudden onset — a mass appeared and all the symptoms disappeared. If it had not been for the mass the patient would not have sought medical advice. The record states that she had an "ulcer of the small intestine." That is a peculiar statement, and I assume that it was made by the patient; a radiologist would probably have specified where the ulcer was. I am inclined to discard the statement as being of no particular value. We should not put too much weight on anything that we have not ourselves observed or proved.

The history also states that she had an anal fistula. I was taught that that can be of tuberculous origin, and to look for tuberculosis elsewhere in the body.

She had amenorrhea, which does not suggest much to me because of her age. I should like to ask Dr. Linton if he would pay any attention to the fact that a woman of this age was not menstruating.

DR. ROBERT R. LINTON: None whatever.

DR. HOLMES: The next point of significance is the character of the mass. On physical examination it was firm, smooth and nontender and did not pulsate; it was movable and shifted with respiration. I consider these observations to be quite important.

The fact that the examiners could not connect it with any particular organ is of little significance.

Among the conditions one has to consider, of course, is an aneurysm. Although pulsation does not prove that a lesion is an aneurysm, the absence of pulsation is of great value. The temperature, pulse, respirations and blood pressure were normal.

I should say that it was ruled out by that method and shall not waste any time on it.

In the examination of the gastrointestinal tract there are several significant things. First is the pressure defect on the lesser curvature of the stomach, which extends into the duodenum and seems to lie nearly in the midportion of the abdomen. The



FIGURE 1

The examination of the blood I also consider to have been within normal limits. Is that true?

DR. LINTON: Yes.

DR. HOLMES: Is there anything in the blood picture to cause a suspicion of lymphoma? That is one of the things that I want to consider.

DR. LINTON: I should think not.

DR. HOLMES: The attending physicians evidently wanted to rule out the urinary tract as a possible source for this mass. Here is the series of films, and

density of the shadow is about the same as that of muscle or liver. There is no shadow of diminished or increased density, which would be of some value. I can make out the liver quite well; it is not enlarged or abnormal in shape, and the abstract tells us that the patient had no esophageal varices. There is nothing suggestive in the small or large bowel. The location of the mass is of some importance: it is above the lesser curvature and rather well over toward the midline. I shall go over these points in detail later.

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DR. ALLEN: Yes; a great deal more so than a pancreatic cyst, which would move only with expiration.

DR. SWEET: This was not so movable as one would expect for a mesenteric cyst; nor did it move so much as the one large hepatoma of the liver that happened to have had and that was presented here two or three years ago.<sup>1</sup>

DR. HOLMES: If this was a mesenteric cyst it must have been in the lesser omentum. I do not believe that a cyst in the greater omentum or in the mesentery of the bowel could have produced such an extensive pressure defect in the stomach.

#### CLINICAL DIAGNOSIS

Tumor of liver ?

Cyst of pancreas ?

#### DR. HOLMES'S DIAGNOSIS

Cyst, probably in tail of pancreas.

#### ANATOMICAL DIAGNOSIS

Islet-cell adenoma of pancreas.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Will you tell us about your operative findings, Dr. Sweet?

DR. SWEET: I should like to say first that Dr. Holmes certainly made an excellent clinical analysis of this case, far better than we did. I decided that it must be a tumor of either the liver or the pancreas. At operation the mass was obviously in the pancreas. It moved with the pancreas the way a carcinoma of the stomach does when it is adherent to the pancreas. The tumor was not pedunculated and could be moved only by moving the entire pancreas; it was part of the body of the pancreas, being located just to the left of the head, close to the duodenum. It was vascular and appeared to be a solid tumor or, if a cyst, an extremely tense one. It was somewhat of a technical stunt to get it off the middle colic vessels without destroying the vascular supply of the duodenum, but it came out, leaving a great hollow in the pancreas. I had never seen anything like it before.

DR. CASTLEMAN: As Dr. Sweet indicated, the specimen we received was circumscribed, with a fairly smooth surface. It was distinctly brownish and, on section, soft and not at all cystic. Microscopic examination showed it to be an adenoma of the islet cells of the pancreas, which apparently had not produced any endocrine disturbance. We went back and questioned the patient about hypoglycemic spells but were unable to elicit any suggestion of one. In Whipple's<sup>2</sup> review of these tumors, he found that the number that were asymptomatic was greater than that of those producing hypoglycemic symptoms.

DR. HOLMES: Was there any evidence of hemorrhage into the tumor?

DR. CASTLEMAN: No.

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#### CASE 31052

#### PRESENTATION OF CASE

A thirty-one-year-old married woman was admitted to the hospital with abdominal cramps.

One month prior to admission the patient missed her expected menstrual period. Four to five days later she began to have vaginal bleeding, passing fresh blood and dark shreds on the first day, followed by intermittent spotting. Her breasts had enlarged and were tender. Twenty-four hours before entry she developed severe cramps in the upper portion of the abdomen. These were quite severe during the night and interfered with sleep. There was no nausea, vomiting, chills, fever or diarrhea. She had had a normal bowel movement on the day prior to admission but none since.

The patient had been admitted to the hospital ten years previously with abdominal cramps. A laparotomy performed at that time revealed a third degree retroversion of the uterus and chronic typhlitis. A ventral suspension of the uterus was done, and the appendix was removed.

She had been married two other times, followed by divorce. During her first marriage eight years previously she had one pregnancy, which was aborted. There were no other pregnancies.

Physical examination on admission revealed a well-developed and well-nourished young woman. The breasts were moderately enlarged and tender, with a widened areola. The heart and lungs were negative. The abdomen revealed diffuse tenderness without spasm but with moderate rebound tenderness in both lower quadrants. No masses were felt. Peristalsis was normal. Pelvic examination revealed a soft uterus of normal size. The fundus was in anterior position and freely movable. The cervix was moderately soft. An irregular, slightly tender mass, 3 to 4 cm. in diameter, was felt in the right adnexal region.

The temperature was 99.8°F., the pulse 66, and the respirations 20. The blood pressure was 110 systolic, 56 diastolic.

Examination of the blood revealed a white-cell count of 13,500. The hemoglobin was 11.8 gm. The urine was essentially negative. A stool examination was negative. A Friedman test for pregnancy was positive.

A roentgenogram of the abdomen revealed an unusual distribution of gas, there being a consider-

Could this patient have had an abdominal aneurysm? There is no sign of arteriosclerosis. The Hinton test was negative, and the tumor did not pulsate. I believe I can drop that. In considering a case, one should always keep in mind the factors that are of interest to the patient. In this particular case the patient wanted to know if she had a lesion that ought to be operated on, and, if so, whether it was going to be a great risk. So we have to rule out aneurysm on that basis; if on no other.

Could she have had a tumor of the liver? It is in the proper place, and it is smooth, round and not lobulated, but she had no varices or signs of cirrhosis; also, there is no evidence of metastases elsewhere in the body. The absence of change in the liver and the absence of esophageal varices make the diagnosis of primary tumor of the liver unlikely. If I had seen this patient on the ward and was making my interpretation from the evidence that we have here, I should say that she did not have a primary tumor of the liver, but at this conference, where many of the rare cases are selected for discussion, this case might be the exception; I do not believe that I can rule out a tumor of the liver.

Could it have been a tumor of the pancreas? It might well have been. The mass is smooth and round and probably cystic. A cyst of the pancreas is not too infrequent. Ordinarily it occurs in the head of the pancreas and does not produce this type of deformity; but occasionally it does. It is not particularly uncommon for tumor in the tail of the pancreas to produce this sort of picture. The duodenum is displaced to the right and downward, and the duodenal loop, instead of being enlarged, is much smaller than it should be. Tumor of the head of the pancreas usually increases the size of the loop rather than diminishes it, but tumor of the tail may not. Therefore, I believe that that is a likely diagnosis. Can tumor of the pancreas cause as few symptoms as this patient had? And is it consistent with the symptoms that she did have? Can you help me on that, Dr. Sweet?

DR. RICHARD H. SWEET: If it were a cyst, I should think so.

DR. HOLMES: Could this have been hydrops of the gall bladder? It is in the correct place. I should expect a hydrops of the gall bladder to displace the whole duodenum downward, but it looks a little too far to the left. But I do not see how I can rule that out on the evidence that we have. Could one have hydrops of the gall bladder with absence of symptoms?

DR. SWEET: I doubt it.

DR. HOLMES: I hope that Dr. Sweet and Dr. Linton are helping me. I have been accused of not helping the surgeons at times.

Could it have been a lymphoma? Lymphomatous masses or a single mass does occur in the belly. Was a careful search made for enlarged lymph nodes elsewhere in the body?

DR. BENJAMIN CASTLEMAN: None were found.

DR. HOLMES: The blood picture was normal. Furthermore, a lymphoma usually is not so round as this mass; it is apt to be lobular. I am going to rule it out on that basis.

On account of the anal fistula, I have to think of tuberculous nodes. There is no calcification in the tumor, and no other calcified nodes are seen elsewhere. I believe that we can rule it out.

We come down to some form of cyst—a cyst in the lesser omentum, a cyst of the pancreas, a dermoid cyst or an echinococcal cyst. Dermoid and echinococcal cysts are likely to contain calcium, but there is no evidence of calcification in this tumor. In addition, the appearance of the lesion and the story make echinococcal cyst seem unlikely. What part of the country did the patient come from?

DR. CASTLEMAN: New England.

DR. HOLMES: Echinococcal cysts are rare in persons who have not been outside New England.

There are two or three things that should have been done during the x-ray examination, provided the radiologist had all the facts that I have. For instance, if this were a dermoid cyst and the patient had a film taken in the upright position, the contents of the cyst might have settled in different layers. Furthermore, there should have been an x-ray examination of the chest to be sure that she did not have metastases. That would help in deciding whether the tumor was benign or malignant.

This could have been a leiomyosarcoma arising in the wall of the stomach. In that case, a careful search for metastases in the lung would have been helpful, as well as an examination in the upright position to see whether the mass could be separated from the stomach. A leiomyosarcoma would be adherent to the stomach, whereas a cyst in the pancreas would not. They may have done all this of course; but there is no record of it.

In conclusion I shall make the most obvious diagnosis, that is, a cyst, probably in the tail of the pancreas. I cannot be absolutely certain that it was not a primary tumor of the liver, but in the absence of cirrhosis of the liver this is extremely rare.

DR. ARTHUR W. ALLEN: I should like to call attention to a sign that Dr. Lincoln Davis discovered several years ago in diagnosing echinococcal cysts. He found that on percussion it gave the same sensation that one would get on percutting an inner spring mattress. This abstract says nothing about percussion, and that might have helped to rule out one possibility.

DR. SWEET: I did not percuss it.

DR. ALLEN: Another interesting feature is that the mass was described as movable and shifting with respiration. It does not say how movable; that would be helpful in differential diagnosis because cysts arising in the mesentery are quite movable.

DR. HOLMES: Would a cyst in the lesser omentum be movable?

case the decidua was so abundant that we seriously considered a diagnosis of uterine pregnancy. The absence of any trace of a chorionic villus, however, should make one suspect some sort of ectopic pregnancy.

In the gross specimen there were, as Dr. Simmons has stated, fibrous nodules near the cornua of the uterus—a condition that has been called “salpingitis isthmica nodosa.” On microscopic examination there were islands of epithelium in gland formation, although they were probably not true glands but pseudoglands. The ordinary explanation of this condition is that some inflammatory process has occurred in the fallopian tube with the formation of a great deal of connective tissue, which pinches off the tortuous epithelial folds, so that they appear as acini in the walls of the tube. Perhaps that is the best explanation for most of these cases. In a recent paper, however, Schenken and Burns,<sup>1</sup> who made serial sections of the entire tube, state that they believe that these little islands of epithelium are not entirely the result of infection

but often due to diverticulosis of the tube, with or without inflammation.

Another explanation of salpingitis isthmica nodosa is that it is endometriosis of the fallopian tube. The glands are similar to the endometrium, but there is no stroma present and most of these patients do not have endometriosis elsewhere.

DR. SIMMONS: It is difficult for me to conceive how this patient could have become pregnant, although Dr. Meigs<sup>2</sup> has described one case of pregnancy in a patient with bilateral salpingitis isthmica nodosa. It must be extremely rare. In most textbooks of gynecology the lesion is described as being due to gonorrhea, tuberculosis or adenomyosis.

DR. CASTLEMAN: Those are the usually accepted causes, but the suggestion of Schenken and Burns that it may be due to diverticulosis is intriguing.

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able amount in the transverse and descending colon but little in the small bowel and stomach.

On the eighth hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. FRANCIS M. INGERSOLL: As I start my discussion there is one premise that I think I shall have to assume, namely, that this patient was pregnant. Certain facts pointing toward it cannot be refuted. The history is compatible. She had a positive Friedman test, and the physical examination also bears out that diagnosis. There are two things that bothered me after reading the case report and that did not seem to fit in with anything that I could think of as a diagnosis. One was that at the time of admission she had severe cramps in the upper abdomen. In my experience that does not fit in with any condition in the pelvis related to a normal pregnancy. The other thing was that I cannot explain the x-ray findings on the basis of pregnancy.

DR. BENJAMIN CASTLEMAN: Dr. Holmes's comment was that reversed peristalsis of the colon at the time the films were taken might have produced such an appearance.

DR. INGERSOLL: Then from the x-ray examination I believe that I shall have to rule out any lesion in the small or large bowel.

The differential diagnosis concerns whether the patient had an extrauterine pregnancy or an intrauterine pregnancy with a threatened miscarriage or an incomplete abortion. Extrauterine pregnancies are relatively frequent, 1 out of every 300 gravid women having one. The setup here is excellent for an ectopic pregnancy. This woman had been married three times and had had one abortion and possibly pelvic inflammatory disease, all of which is an excellent cause for an extrauterine pregnancy. So the first possibility that comes to me is that this mass that was felt in the abdomen was due to an ectopic pregnancy, possibly in the tube. It might have been one of the rare pregnancies that occur in the ovary, the ovum being fertilized just as it is discharged from the ovary, with implantation taking place there. It is possible that the patient had a tubal abortion at the time of the severe pain and that the ovum was outside the tube and actually attached to the large bowel, irritating it and causing a reflux of gas back into the transverse colon, as Dr. Holmes described.

The possibilities other than extrauterine pregnancy are those associated with an incomplete miscarriage. For example, she could have had an incomplete miscarriage to account for the way the uterus felt, and the mass that was felt on the right side could have been inflammatory, — a tubo-ovarian abscess, — although it is quite rare to have a patient with both pregnancy and a real abscess in the tube and ovary. The right-sided mass might have been

an endometrioma; she was thirty-one years of age and had never had a full-term pregnancy. The other thing that occurred to me is that this patient might have had a normal intrauterine pregnancy together with a small cyst of the ovary that had twisted, thus destroying the corpus luteum and producing a miscarriage.

In summary, I shall say that the patient was pregnant and that either the pregnancy was ectopic or she had an incomplete miscarriage, with some other associated phenomenon. If I had to commit myself to one diagnosis, it seems to me that this whole case fits in best with an extrauterine pregnancy, and since this is a clinicopathologic case, in which one expects the unusual, I shall postulate that the extrauterine pregnancy was implanted on the ovary.

DR. FRED A. SIMMONS: The patient was sent to me by an obstetrician because of sterility; she had been married to her third husband for three years. The first time that I examined her, there was a mass on the right side, but it did not change in the subsequent five or six weeks. It took a long time to convince me that it was a tubal pregnancy. At the first visit to the office her menstrual period was a day or two overdue and I assumed that she was pregnant. Following amenorrhea for eight or ten days she then started to flow. Since I thought it was a normal pregnancy, I tried to maintain it by bedrest and so forth. Then when she developed cramps, I sent her into the hospital.

On the fourth hospital day she passed a piece of tissue 1 cm. wide and 4 cm. long, which I immediately assumed was produced by conception. It was sent to the laboratory, where a diagnosis of decidua without chorionic villi was made, which means ectopic pregnancy.

### CLINICAL DIAGNOSIS

Tubal pregnancy.

DR. INGERSOLL'S DIAGNOSIS

Ectopic pregnancy, possibly in ovary.

### ANATOMICAL DIAGNOSES

Tubal pregnancy.

Salpingitis isthmica nodosa, bilateral.

### PATHOLOGICAL DISCUSSION

DR. SIMMONS: The patient was operated on, and we found a tubal pregnancy on the right. She had in addition a lesion in the isthmic portion of both tubes that grossly suggested salpingitis isthmica nodosa.

DR. CASTLEMAN: How much blood did she have in the peritoneal cavity?

DR. SIMMONS: About 40 cc.

DR. CASTLEMAN: One interesting point, which Dr. Simmons mentioned, is the presence of decidua in the uterus in cases of ectopic pregnancy. In this

medicine is being subjected to criticism. Every member of the Massachusetts Medical Society should do all within his power in an attempt to bring about the defeat of these bills.

### A NEW AND RAPID LABORATORY TEST FOR SMALLPOX

MAJOR VAN ROOYEN and Major Illingworth,<sup>1</sup> of the Royal Army Medical Corps, have recently contributed what appears to be a most valuable laboratory test for smallpox. According to them, a smear preparation from a suspected case of smallpox can be made, stained and examined and the report handed to the physician in half an hour. The material is obtained by delicately scraping either the base of a vesicle or, still better, an early papule without drawing blood. This is rubbed onto a specially prepared slide, stained according to the Paschen method (which is described in detail) and examined under the microscope. If the material was secured from a case of smallpox, the trained eye quickly detects masses of characteristic elementary bodies. Not only are these infinitely more numerous than the elementary bodies found in chicken pox<sup>2</sup> but they are about twice as large. The authors warn that this method applies only to the identification of smallpox bodies and is not applicable to those of chicken pox, since the latter are too scanty.

The test was positive in 77 cases of smallpox and negative in only 3. In no case did a positive test disagree with the clinical diagnosis. The test proved particularly valuable in the early diagnosis of cases of modified smallpox, in which only a few discrete lesions, suggestive of chicken pox, were present and also in the early stages of the severe forms of hemorrhagic smallpox in which the papular stage suggested typhus fever or measles. Indeed, in the latter type of case the earliest buccal lesions often resembled Koplik spots. The importance of this test can best be appreciated by realizing that the Paul test, in which infective material is scratched into a rabbit's cornea, can only be completed in three days and that the same applies to the chick chorioallantoic-membrane test, whereas the floccu-

lation test is not reliable until after the first week of the disease.

In another contribution Major Illingworth and Major Oliver<sup>3</sup> report their observations on an epidemic of smallpox in Egypt during 1943 and 1944. These authors emphasize that the early clinical differentiation of smallpox and chicken pox was often impossible. Not only was the typical distribution of the lesions ("centrifugal" and "centripetal," respectively) a snare and a delusion, but they also found that smallpox lesions came out in crops over a period of four or five days, a characteristic usually ascribed to the lesions of chicken pox, and that maturation of the lesions was sometimes quite as rapid in smallpox as in chicken pox. They noted oval lesions in the folds of the skin and petechiae in the axillas in cases of the hemorrhagic type. Even the characteristic backache of the prodromal stage of smallpox was by no means a prominent symptom. Finally, 96 of the 100 patients in the series had been previously vaccinated, 70 having been vaccinated "successfully" within two years.

All this goes to show that there are exceptions to every point of differentiation between smallpox and chicken pox, as was brought out in a recent progress review in the *Journal*.<sup>4</sup> Smallpox varies in character and severity in different localities. Under wartime conditions as they exist today in Egypt, with the influx of troops from so many parts of the world, this disease in almost every hue of human skin presents extraordinary difficulties. Faced with these, the authors found that examination of the scrapings from papules or vesicles for elementary bodies was of the greatest assistance in making an early diagnosis.

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3. Illingworth, R. S., and Oliver, W. A. Smallpox in Middle East. *Lancet* 247:681-685, 1944.
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### MASSACHUSETTS MEDICAL SOCIETY

#### DEATH

HERBERT — Edward Herbert, M.D., of Fall River, died June 26. He was in his seventieth year.

Dr. Herbert received his degree from Columbia University College of Physicians and Surgeons, New York, in 1902. He was a fellow of the American Medical Association.

# The New England Journal of Medicine

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## STANDARDS OF MEDICAL EDUCATION

ON JANUARY 5, 1945, the failure of the Massachusetts Approving Authority to accredit the Middlesex University School of Medicine was upheld by the Superior Court of Suffolk County.

The law establishing the Approving Authority was signed by the Governor of Massachusetts, James M. Curley, in 1936. A photograph taken at the time he signed the bill shows several members of the Massachusetts Medical Society watching the proceedings with great interest, among them being Dr. Charles E. Mongan, who at that time was president of the Society and had much to do with the campaign to enact the legislation. Also in the group was the present dean of the Middlesex University

School of Medicine, Dr. Stephen Rushmore, who then was secretary of the Board of Registration in Medicine and automatically became a member of the Approving Authority.

Soon after its establishment, the Approving Authority drew up the seventeen qualifications that a medical school must meet in order to be approved. These qualifications are the same as those used to measure the quality of the schools that have recently applied for approval, and it was the failure of the Middlesex University School of Medicine to meet all the qualifications that made it necessary for the present Approving Authority to deny approval. This denial followed three inspections by three different groups comprising the Approving Authority and a public hearing held in July, 1944.

The law passed in 1936 stated that students who matriculated at a medical school on or after January 1, 1939, must graduate from a school accredited by the Approving Authority in order to be eligible to take the examination for registration in this state. The law was amended in 1939, the effective date being changed to January 1, 1941. Students coming under this classification began to graduate from medical schools during the summer of 1944, and those who had received their diplomas from schools not approved by the Approving Authority have been denied the right of examination by the Board of Registration in Medicine. Massachusetts has three such schools, namely, the Middlesex University School of Medicine, the Massachusetts College of Osteopathy and the College of Physicians and Surgeons. The last two have never asked for approval.

At long last the practice of medicine in the Commonwealth is open only to those men and women who have been properly trained, and Massachusetts need no longer be called "the dumping ground" for medical-school graduates; but a number of bills that aim either to abolish the Approving Authority or to postpone again the date of its effectiveness have already been introduced for the consideration of the present session of the General Court. The passage of such legislation can either halt or stop forever the progress toward higher medical standards, and high standards of medical education *must* be maintained in these days when the practice of

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## THE DIAGNOSIS OF POSTERIOR HERNIATION OF THE LUMBAR INTERVERTEBRAL DISKS\*

DONALD MUNRO, M.D.†

BOSTON

IT IS common knowledge that there is considerable difference of opinion in the medical profession concerning the methods and efficiency of the treatment of posterior protrusions of the nucleus pulposus from ruptured lumbar intervertebral disks. Underlying this there is an even greater divergence of views about the criteria that must be met before diagnosing this condition.

In a recent group of papers, Magnuson<sup>1</sup> points out that a fine differential diagnosis is necessary in low-back cases and that the recent neurosurgical approach to this diagnostic problem, which has been made "mainly from this standpoint of root pressure from a ruptured intervertebral disk, . . . , seems much too narrow." He points out that variations in the size of the intervertebral foramina and local joint disease cause the low-back pain and associated sciatica that is generally ascribed to disk herniations. He also makes the important statement that it is always possible through an incision in the annulus to curette or otherwise bring out the material that forms the disk, and he is much opposed to incising the intact annulus as part of an exploration for a suspected disk. Larmon<sup>2</sup> offers substantiating evidence from anatomic dissection. Caldwell<sup>3</sup> discusses spondylolisthesis and spondylolysis as frequent causes of low-back pain, either alone or associated with sciatica, and holds that a compressed root is usually the cause of such symptoms and that it is the decompression of the involved root that is the significant therapeutic procedure. Dandy<sup>4</sup> has evolved a so-called "concealed disk" that he claims may afflict all the lumbar intervertebral spaces. He appears to believe that the diagnosis of herniation of a lumbar disk presents no problems. In patients with this disease he states that the history is almost pathognomonic, that the localization is perfectly simple and certain, that diagnostic intraspinal injections are not only

unnecessary but ineffective in over two thirds of the cases and that lumbar puncture is needful only if the presence of a tumor of the spinal cord is suspected. It appears, however, that such disks are so well concealed that they can be demonstrated only during operation, and that the indications for surgical interference are the broad ones of an operable patient with a sore back and pain in the leg. Keegan<sup>5</sup> contends that single nerve roots compressed by herniated disks cause dermatome hypalgesia that is accurately diagnostic of the location and level of the lesion. He states that a conservative attitude should be taken in their treatment because in many early cases improvement occurs without intervention. French and Payne<sup>6</sup> report 8 cases — to which I can add 1 of rupture of the third lumbar disk, included in the series reported below — of tumorlike compression of the cauda equina by a herniated disk. All his cases as well as the one from my clinic had a complete or virtually complete dynamic subarachnoid block with a high cerebrospinal-fluid protein level and symptoms of cauda equina, rather than of single root, involvement. There was a long history in every case (five years in mine), and there was every reason to suppose that the surgery that was eventually made available would have been more successful had the diagnosis been made and treatment instituted much earlier in the course of the disease. Oppenheimer,<sup>7</sup> on the basis of roentgenologic experience and a study of the literature, has evolved the term "discogenic disease" to cover a wide variety of signs and symptoms, including pain at all levels of the spine and associated with recurrent attacks of pain in the arm and leg. He makes the statement that disk lesions are about twice as frequent as duodenal ulcer. In contrast to this, Breck, Hillsman and Basom<sup>8</sup> found that 15 per cent of applicants for heavy work at the plant in Texas where the survey was made had to be rejected because of disease of the lumbosacral spine. This was demonstrated in 450 consecutive pre-employment roentgenograms made in patients without backache either at the time they were seen

\*From the Neurological Board.  
Read before the Neurological Board.  
and Commission.

†Assistant professor of neurosurgery, Harvard Medical School, associate professor of neurosurgery, Boston University School of Medicine, chief, Department of Neurosurgery, Boston City Hospital.

# MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

## COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1944

### RÉSUMÉ

DISEASES	DECEMBER 1944	DECEMBER 1943	SEVEN-YEAR MEDIAN
Anterior poliomyelitis.....	11	14	2
Chancroid.....	5	0	*
Chicken pox.....	1407	1618	1603
Diphtheria.....	29	32	19
Dog bite.....	517	431	561
Dysentery, bacillary.....	12	105	16
German measles.....	89	118	68
Gonorrhea.....	373	477	335
Granuloma inguinale.....	5	0	*
Lymphogranuloma venereum.....	2	0	*
Malaria.....	42	11	0
Measles.....	235	1320	1082
Meningitis, meningococcal.....	26	60	7
Meningitis, Pfeiffer-bacillus.....	7	3	2
Meningitis, pneumococcal.....	9	7	†
Meningitis, staphylococcal.....	—	—	†
Meningitis, streptococcal.....	—	1	†
Meningitis, other forms.....	1	4	†
Meningitis, undetermined.....	1	5	†
Mumps.....	1353	670	597
Pneumonia, lobar.....	233	576	407
Salmonella infections.....	5	5	4
Scarlet fever.....	1052	978	926
Syphilis.....	373	560	475
Tuberculosis, pulmonary.....	174	194	241
Tuberculosis, other forms.....	6	18	26
Typhoid fever.....	6	2	5
Undulant fever.....	3	3	3
Whooping cough.....	466	341	784

\*Made reportable in December, 1943.

†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

### COMMENT

Diphtheria continues at a relatively high level — approximately at one and a half times the seven-year median. This indicates, of course, that local immunization effort should be stepped up.

Mumps continues its gradual climb toward higher levels, and scarlet fever is again on the increase after a few months of lower prevalence. Measles and lobar pneumonia, on the other hand, have dropped to almost record low levels.

Malaria is now regularly appearing in the reports of certain boards of health, but this is due to the presence in Massachusetts of service men and others who have acquired the disease in foreign service.

### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Arlington, 1; Boston, 3; Hadley, 1; Holyoke, 1; Newton, 1; Oxford, 1; Waltham, 1; Wellesley, 1; West Springfield, 1; total, 11.

Diphtheria was reported from: Barnstable, 4; Boston, 6; Bourne, 1; Falmouth, 1; Lowell, 1; Medford, 1; New Bedford, 4; Rockland, 1; Salem, 1; Somerville, 7; Wakefield, 1; Weymouth, 1; total, 29.

Dysentery, bacillary, was reported from: Amherst, 2; Everett, 1; Lowell, 1; Malden, 4; Medford, 2; Northampton, 1; Quincy, 1; total, 12.

Encephalitis, infectious, was reported from: Medford, 1; Winchendon, 1; total, 2.

Malaria was reported from: Amesbury, 1; Camp Edwards, 9; Cushing General Hospital, 3; Dedham, 1; Easton, 1; Everett, 1; Hardwick, 1; Haverhill, 2; Ipswich, 1; Marlboro, 1; Newton, 2; Quincy, 1; Regional Hospital, Waltham, 16; Somerville, 1; Stoneham, 1; total, 42.

Meningitis, meningococcal, was reported from: Arlington, 1; Attleboro, 1; Boston, 8; Bridgewater, 1; Fall River, 2; Framingham, 1; Gloucester, 1; Haverhill, 1; Lawrence, 1; Lynn, 1; Malden, 1; Medford, 1; Melrose, 1; Newton, 1; Saugus, 1; Somerville, 1; Weymouth, 1; Worcester, 1; total, 26.

Meningitis, Pfeiffer-bacillus, was reported from: Arlington, 1; Boston, 2; Cambridge, 1; Hanson, 1; Medford, 1; Watertown, 1; total, 7.

Meningitis, pneumococcal, was reported from: Boston, 1; Brockton, 1; Chicopee, 1; Lawrence, 1; Lynn, 1; Marion, 1; Medford, 1; Springfield, 1; Westport, 1; total, 9.

Meningitis, other forms, was reported from: Boston, 1; total, 1.

Meningitis, undetermined, was reported from: Boston, 1; total, 1.

Salmonella infections were reported from: Lawrence, 2; North Andover, 1; Somerville, 1; Southbridge, 1; total, 5.

Septic sore throat was reported from: Avon, 2; Belmont, 1; Boston, 14; Marion, 1; Medford, 1; Merrimac, 1; Revere, 1; total, 21.

Tetanus was reported from: Medway, 1; total, 1.

Trachoma was reported from: Lee, 1; Watertown, 1; total, 2.

Trichinosis was reported from: Boston, 4; total, 4.

Typhoid fever was reported from: Boston, 2; Haverhill, 1; Lawrence, 1; Tewksbury, 1; Warren, 1; total, 6.

Typhus fever was reported from: Boston, 1; total, 1.

Undulant fever was reported from: Boston, 1; Bourne, 1; Sheffield, 1; total, 3.

## CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Lowell	February 2	Albert H. Brewster
Salem	February 5	Paul W. Hugenberger
Haverhill	February 7	William T. Green
Brockton	February 8	George W. Van Gorder
Worcester	February 16	John W. O'Meara
Pittsfield	February 19	Frank A. Slowick
Springfield	February 21	Garry deN. Hough, Jr.
Fall River	February 26	Eugene A. McCarthy
Hyannis	February 27	Paul L. Norton

## NOTICES

### JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a.m.

### MEDICAL CONFERENCE PROGRAM

Friday, February 2 — Medical Disorders in Pregnancy. Dr. Lewis Dexter.  
Tuesday, February 6 — Neuro-Hormonal Factors in the Origin and Treatment of Cardiovascular Disease. Dr. W. Raab.  
Wednesday, February 7 — My Recent Trip to the West Indies. Dr. William Dameshek.  
Friday, February 9 — Erythrocyte Preservation. Dr. Joseph F. Ross.  
Wednesday, February 14 — Bronchiectasis: Medical and surgical aspects. Dr. Bert Cotton.  
Friday, February 16 — Dwarfism. Dr. Nathan Talbot.  
Wednesday, February 21 — Interesting Effects on Lungs and Air Passages of Breathing Extremely Hot or Cold Air. Dr. Alan R. Moritz.  
Friday, February 23 — Protein Nutrition in Problems of Medical Interest. Dr. Fredrick J. Stare.  
Wednesday, February 28 — Penicillin in Venereal Disease. Dr. Oscar F. Cox.

On Monday mornings clinics will be given by Dr. Samuel Proger. On Saturday mornings clinics will be given by Dr. William Dameshek. On Tuesday and Thursday mornings Dr. S. J. Thannhauser will give medical clinics on hospital cases.

### MASSACHUSETTS PHYSIOTHERAPY ASSOCIATION

The next meeting of the Massachusetts Physiotherapy Association will be held at the Women's Educational and Industrial Union on Tuesday, February 6. At 7:00 p.m., following a dinner and business meeting, Miss Margaret Arey, supervising instructor in public-health nursing in orthopedics in Massachusetts, will talk on the subject "The Care of Patients with Amputations."

### HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of the Peter Bent Brigham Hospital on Tuesday, February 13, at 8:15 p.m.

### PROGRAM

Clinical case presentation from the Boston City Hospital.  
The Distribution of Lipids in Blood Cells and Plasma.  
Drs. F. F. Foldes and A. J. Murphy.  
Histochemical Studies of the Retina. Dr. C. B. Anfinsen.  
Studies on Recently Isolated Influenza Viruses. Drs. J. P. Enders, M. Finland, E. G. Mills and M. W. Barnes.

(Notices continued on page xix)

ANALYSIS OF RESULTS

Age and Sex Incidence

Table 1 shows the age and sex distribution in each series. The latter was about the same in both series. Furthermore, 85 per cent of the proved herniation cases occurred between the ages of twenty and fifty, compared with 83 per cent for similar conditions. Thus, it cannot be said from my experience that the age and sex of a patient

lifting strain, a back injury or a fall weights the diagnostic scales in favor of a herniation as against similar conditions. A complete absence of a history of injury neither favors nor militates against a diagnosis of herniation. The relation to injury in industry is of no diagnostic significance.

Time Relations

In Table 3 are analyzed the intervals elapsing between the first attack of pain and hospitalization

TABLE 1. Sex and Age Incidence.

- SERIES	SEX		AGE							LOWEST	HIGHEST
	M	F	1-10 yr.	10-20 yr.	20-30 yr.	30-40 yr.	40-50 yr.	50-60 yr.	60-70 yr.	yr.	yr.
Proved herniations	58	20	0	2	11	29	26	7	3	17	67
Similar conditions	31	10	0	0	5	13	16	7	1	26	66

with pain in the back or leg is of any aid in the differential diagnosis of a herniated lumbar disk.

Etiology

Table 2 shows the comparative figures for the type of injury, including the number and percentage of injuries received in industry. Certain of these findings should be emphasized. For example, it was as usual for a herniation of a lumbar disk to develop in the absence of any history of injury as it was for it not to do so. This agrees with the findings of Bradford and Spurling.<sup>10</sup> Love,<sup>11</sup> how-

and those between the start of the attack that led the patient to seek relief at the Boston City Hospital. These figures are neither helpful nor significant from the point of view of differential diagnosis. They do demonstrate, however, the extraordinary length of time that a patient is willing to suffer before seeking or consenting to hospitalization.

Symptoms and Signs

The foregoing are more or less routine considerations in the analysis of any such series. The analysis of subjective symptoms and objective signs (Tables

TABLE 2. Etiology.

TYPE OF INJURY	PROVED HERNIATIONS				SIMILAR CONDITIONS			
	TOTAL NO OF CASES	PERCENTAGE OF GROUP	NO OF INDUSTRIAL CASES	PERCENTAGE OF INDUSTRIAL CASES	TOTAL NO OF CASES	PERCENTAGE OF GROUP	NO OF INDUSTRIAL CASES	PERCENTAGE OF INDUSTRIAL CASES
No injury	8	10	0	0	5	12	0	0
Automobile accident	3	4	0	0	4	10	0	0
Fall . . . . .	19	24	10	52	7	17	4	57
Lifting strain	20	26	15	75	5	12	5	100
Back injury	17	22	11	65	3	7	2	67
Postoperative	0	0	0	0	12	29	10	83
Change of position	5	6	3	60	2	5	1	50
Others	6	8	0	0	3	7	0	0
Totals . . . . .	78		39		41		22	
Percentages . . . . .				50				53

ever, states that there is usually a history of trauma or unusual stress or strain to the back. Lifting strain was twice as frequent a cause of herniation as of similar conditions, back injuries were three times as frequent, and falls were one and a half times as frequent. The incidence of industrial cases for each type of injury was approximately the same in both series except that all the cases with similar conditions caused by lifting strain were industrial whereas only three quarters of the cases with herniation from the same cause were industrial. There were no postoperative cases in the proved series, and there was no significant difference in industrial distribution between the two series as a whole. Other things being equal, a history of a

4 and 5) is of more interest and significance. The subjective symptoms of pain have been analyzed in some detail because pain is unquestionably the most significant symptom of herniated lumbar disks. The first attack of pain occurred most frequently in the back, where a disk had herniated or was about to herniate or where some similar condition was present or was about to develop (Table 4). The difference in frequency is not great and is probably not significant diagnostically, the frequency being only 10 per cent higher in the proved disk cases than in the other conditions. The number of cases in which pain was absent in the back at the first attack but occurred instead in the leg or legs, including the hip and thighs, should be noted. The

or previously. Finally, Shinnors and Hamby<sup>9</sup> make the statement that claim adjusters of at least one insurance company are known to discourage compensation patients disabled by protruded intervertebral disks from seeking surgical relief, and there is certainly a well-founded but undocumented belief that other insurance companies, members of industrial accident boards and of the medical departments of the Army and Navy and many members of the civilian medical profession regard the diagnosis of herniation of a lumbar intervertebral disk with considerable skepticism until the weight of evidence in its favor is overwhelming.

My experience has led me to believe that the clinical diagnosis of a posterior herniation of the nucleus pulposus of a ruptured lumbar intervertebral disk that is based only on the history and physical and neurologic examinations, if unconfirmed by other objective findings, is at best only a "possible" one. Such a low level of accuracy is certainly not ideal. Moreover, even if greater accuracy were possible and the means used to obtain it were safe, it would still not be in the best interests of the patient to advise operative interference on this basis in the usual case and in the absence of an emergency, nor could one expect the patient to accept such advice without demur. Indeed we should scarcely be willing to do so ourselves. The continued search for a substance that visualizes these lesions with a reasonable degree of accuracy and that is simple and safe, as well as the continued use of admittedly unsatisfactory mediums designed for this purpose, emphasizes the general recognition by the medical profession of the need for improvement in diagnostic accuracy and their distrust of unconfirmed clinical criteria. It is the primary purpose of this paper to present evidence to support this contention. Secondly, I wish to make a brief preliminary report on a new substance to be used for visualization of the lumbar subarachnoid space that so far has met all the requirements noted above. This substance is 20 per cent Skiodan.

So far as I am aware, the best statement of the requirements that must be met before a clinical diagnosis of posterior herniation of the lumbar disks can be made is that published by Bradford and Spurling.<sup>10</sup> More recently Love<sup>11</sup> has also listed essentially the same requirements. They comprise a history of trauma or of unusual strain to the back, with subsequent intractable backache or sciatic pain, or both. The back pain usually precedes the leg pain. The pain is said to be intermittent and not relieved by the ordinary therapeutic procedures. On examination the spinal muscles are spastic, spinal motion is limited and painful, and the straight-leg-raising test is positive. Neurologic signs are often minimal. They include absence or diminution of one Achilles reflex and variable areas of altered sensation in the affected extremity. Bradford and Spurling state that the latter occurs in

75 per cent of the cases examined and that numbness and paresthesias in the lateral aspect of the leg and foot are frequent. They also differentiate a herniation of the fourth and the lumbosacral disk by the distribution of the sensory loss, especially with reference to the great and other toes, and by changes in the ankle jerk. They lay great stress on the jugular-compression test and the effects on the pain of coughing, sneezing or straining, as well as the diagnostic conclusions that may be drawn from these findings. It is generally recognized that herniations may occur at any level of the lumbar spine and may be multiple. Bradford and Spurling, as well as Love, advocate the use of contrast mediums as an aid to diagnosis, but the former writes, "There has been unwarranted emphasis on the difficulty of recognizing clinically cases of herniated nucleus pulposus," and the latter states, "In the majority of cases . . . the diagnosis can be accurately made on the basis of the history and physical findings."

#### MATERIAL

In an attempt to verify these statements, I have analyzed two parallel series of cases in which the history and physical findings might be generally considered to justify a diagnosis of herniation of a lumbar disk. In one series of 78 cases a herniation was proved to have been present by operation and by pathological examination of the removed material in all but 3 cases, which had unmistakable and characteristic myelogram deformities. The comparable series was made up of 41 cases with the following diagnoses: suspected ruptured intervertebral disk, 13 cases (proved negative by operation in 10); compressed root from a small dural envelop or local scar or resulting from a fractured lumbar vertebra, 19 cases (in 14 of which the diagnosis was verified by operation); questionable radiculitis, the cause of which was not apparent, 4 cases (verified by operation in all); a congenital defect without other demonstrable disease, 2 cases (verified by operation in both); and back strain, 3 cases (verified by operation in 1). Of 9 cases listed above as not having been verified by operation, an abdominal aortic aneurysm was visible by x-ray in 1. There was a negative myelogram in this case. In 1 case there were four negative myelograms; operation was not performed in spite of a so-called "typical history." In 1 there was an unquestionably positive myelogram and operation was offered but refused. Five patients had had herniated disks previously removed elsewhere, only to have the symptoms recur in from four to eleven months thereafter. In 2 of these cases the myelogram was positive (abnormal but not characteristic of herniation), and in 1 it was negative. All 5 patients are awaiting re-operation. The last patient had a suggestive clinical history and examination and a questionable myelogram and has refused operation.

ANALYSIS OF RESULTS

Age and Sex Incidence

Table 1 shows the age and sex distribution in each series. The latter was about the same in both series. Furthermore, 85 per cent of the proved herniation cases occurred between the ages of twenty and fifty, compared with 83 per cent for similar conditions. Thus, it cannot be said from my experience that the age and sex of a patient

lifting strain, a back injury or a fall weights the diagnostic scales in favor of a herniation as against similar conditions. A complete absence of a history of injury neither favors nor militates against a diagnosis of herniation. The relation to injury in industry is of no diagnostic significance.

Time Relations

In Table 3 are analyzed the intervals elapsing between the first attack of pain and hospitalization

TABLE 1. Sex and Age Incidence.

- SERIES	SEX		1-10 yr	10-20 yr	20-30 yr	30-40 yr	AGE				LOWEST yr.	HIGHEST yr.
	M	F					40-50 yr.	50-60 yr.	60-70 yr.			
Proved herniations	58	20	0	2	11	29	26	7	3		17	67
Similar conditions	31	10	0	0	5	13	16	7	1		26	66

with pain in the back or leg is of any aid in the differential diagnosis of a herniated lumbar disk.

Etiology

Table 2 shows the comparative figures for the type of injury, including the number and percentage of injuries received in industry. Certain of these findings should be emphasized. For example, it was as usual for a herniation of a lumbar disk to develop in the absence of any history of injury as it was for it not to do so. This agrees with the findings of Bradford and Spurling.<sup>10</sup> Love,<sup>11</sup> how-

and those between the start of the attack that led the patient to seek relief at the Boston City Hospital. These figures are neither helpful nor significant from the point of view of differential diagnosis. They do demonstrate, however, the extraordinary length of time that a patient is willing to suffer before seeking or consenting to hospitalization.

Symptoms and Signs

The foregoing are more or less routine considerations in the analysis of any such series. The analysis of subjective symptoms and objective signs (Tables

TABLE 2. Etiology.

TYPE OF INJURY	PROVED HERNIATIONS				SIMILAR CONDITIONS			
	TOTAL NO OF CASES	PERCENTAGE OF GROUP	NO OF INDUSTRIAL CASES	PERCENTAGE OF INDUSTRIAL CASES	TOTAL NO OF CASES	PERCENTAGE OF GROUP	NO OF INDUSTRIAL CASES	PERCENTAGE OF INDUS TRIAL CASES
No injury	8	10	0	0	5	12	0	0
Automobile accident	3	4	0	0	4	10	0	0
Fall .	19	24	10	52	7	17	4	57
Lifting strain	20	26	15	75	5	12	5	100
Back injury	17	22	11	65	3	7	2	67
Postoperative	0	0	0	0	12	29	10	83
Change of position	5	6	3	60	2	5	1	50
Others	6	8	0	0	3	7	0	0
Totals .	78		39		41		22	
Percentages .				50				53

ever, states that there is usually a history of trauma or unusual stress or strain to the back. Lifting strain was twice as frequent a cause of herniation as of similar conditions, back injuries were three times as frequent, and falls were one and a half times as frequent. The incidence of industrial cases for each type of injury was approximately the same in both series except that all the cases with similar conditions caused by lifting strain were industrial whereas only three quarters of the cases with herniation from the same cause were industrial. There were no postoperative cases in the proved series, and there was no significant difference in industrial distribution between the two series as a whole. Other things being equal, a history of a

4 and 5) is of more interest and significance. The subjective symptoms of pain have been analyzed in some detail because pain is unquestionably the most significant symptom of herniated lumbar disks. The first attack of pain occurred most frequently in the back, where a disk had herniated or was about to herniate or where some similar condition was present or was about to develop (Table 4). The difference in frequency is not great and is probably not significant diagnostically, the frequency being only 10 per cent higher in the proved disk cases than in the other conditions. The number of cases in which pain was absent in the back at the first attack but occurred instead in the leg or legs, including the hip and thighs, should be noted. The



patient's description of the location of the pain during the course of the disease pointed to the leg, exclusive of the foot, as the preponderant location, and to the lower leg as the most frequent site. This

33 per cent in the other series. Pain was increased by coughing, sneezing or straining in 63 per cent of the proved herniation series, as against 40 per cent in the other series, and exercise was more

TABLE 3. *Interval before Hospitalization.*

LENGTH OF INTERVAL	PROVED HERNIATIONS				SIMILAR CONDITIONS			
	FROM FIRST ATTACK TO HOSPITALIZATION		FROM FIRST ATTACK TO HOSPITALIZATION		FROM FIRST ATTACK TO HOSPITALIZATION		FROM FIRST ATTACK TO HOSPITALIZATION	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
Less than 1 wk.	0	0	0	0	1	2	2	5
Less than 2 mo.	4	5	22	28	4	10	11	27
Less than 7 mo.	27	35	64	82	10	24	23	56
Less than 1 yr.	39	50	72	92	17	41	27	66
Less than 2 yr.	45	58	78	100	20	49	31	76
Less than 5 yr.	54	69	—	—	31	76	36	88
Less than 10 yr.	63	81	—	—	34	83	—	—
10 yr.	3	—	—	—	—	—	—	—
12 yr.	3	—	—	—	—	—	—	—
13 yr.	—	—	—	—	2	—	—	—
15 yr.	2	—	—	—	1	—	—	—
17 yr.	1	—	—	—	—	—	—	—
22 yr.	1	—	—	—	—	—	—	—
23 yr.	1	—	—	—	—	—	—	—
24 yr.	—	—	—	—	1	—	—	—
26 yr.	1	—	—	—	—	—	—	—
No pain	—	—	—	—	1	—	1	—
Not given	3	—	—	—	2	—	4	—
Totals	78	—	78	—	41	—	41	—

applies to both series. The infrequency with which the foot and especially the toes are involved is in disagreement with the usual description of the symptoms of herniated lumbar disk. There is

frequently mentioned in the nonherniated series a causing increased pain. As would be expected, rest and orthopedic treatment were the most effective means of decreasing the pain in both series. From

TABLE 4. *Data on Subjective Pain.*

DATA	PROVED HERNIATIONS	SIMILAR CONDITIONS	DATA	PROVED HERNIATIONS	SIMILAR CONDITIONS
Site of first attack of pain:			Site of pain during hospitalization:		
Back	56	25	Low back	57	28
Leg or legs	14	3	Gluteal region	11	5
Back and legs	2	4	Leg:		
Hip and thigh	9	4	Thigh	28	10
Abdomen	2	1	Upper leg	29	17
Sciatic nerve	3	0	Posterior thigh	23	12
No pain	0	3	Posterior lower leg	26	11
Not given	2	1	Lower leg	43	17
			Knee	12	5
			Ankle	15	9
Kind of pain:			Foot:		
Paresthesia	16	1	Foot	13	6
Numbness	32	15	Little toes	8	1
Hypesthesia	3	2	Great toe	2	1
Causalgia-like	1	0	Sole	2	0
Ache	20	30	Abdomen	1	2
Stabbing	14	9	No back pain	20	10
Severe	62	28	No leg pain	1	6
Mild	0	8	No pain	0	3

nothing in these figures that is otherwise of aid in the differential diagnosis of herniation. The pain when present was most frequently described as a constant severe ache and was often associated with subjective numbness. Intermittent pain during the attack was only about one third as frequent as the constant type in both series (Table 5). In 64 per cent of the proved herniations there was a history of recurrent attacks of pain, as compared with

these data it seems reasonable to conclude that a history of recurrent attacks of pain in the lower back and leg, which occur first as pain in the low back and are increased by coughing, sneezing or straining and relieved by rest or orthopedic treatment, is somewhat more indicative of a herniation of a lumbar disk than it is of any similar condition. Subjective symptoms as described by the patient appear to be of no value in identifying the level at

which the disk is ruptured, provided such a rupture is present.

The results of certain objective tests are listed in Table 6. No claim is made that they are com-

come for diagnosis to the general surgeon and not to the specialist. The demonstration of borderline sensory changes, for example, may depend quite as much on the examiner as on the patient, and an

TABLE 5 Data on Subjective Symptoms.

DATA			DATA		
PROVED HERNIATIONS			PROVED HERNIATIONS		
SIMILAR CONDITIONS			SIMILAR CONDITIONS		
Frequency of pain			Cause of decreased pain		
Constant	36	24	Walking	3	2
Occasional	2	3	Standing	1	0
Intermittent	10	8	Sitting	2	10
Attacks of pain			Lying	26	13
Recurrent	49	13	Back motion	0	0
Constant	29	26	Exercise	1	1
Not noted	1	2	Rest	1	—
Cause of increased pain			Local applications	0	—
Cough and so forth	45	14	Heat	3	—
Walking	4	17	Cold	0	—
Standing	14	14	Baking and massage	2	—
Sitting	18	8	Drugs	1	—
Lying	13	3	Osteopathy	1	—
Back motion	42	22	Orthopedic treatment	24	15
Exercise	12	21	Others	4	3
Lifting	8	9	No decrease	0	6
Orthopedic treatment	2	0	No pain	0	3
No increase	3	2	Not noted	23	5
No pain	0	3			
Not noted	7	4			

pletely accurate, and it is impossible to prove that the figures might not have been different had the tests been done by other examiners. I believe, however, that whatever error exists is not large enough

ankle jerk that is considered diminished by a general surgeon will be recognized by the neurologist as normal and only apparently changed because of the method of its elicitation. So, too, whereas an

TABLE 6. Data on Objective Signs.

DATA							DATA						
PROVED HERNIATIONS							PROVED HERNIATIONS						
POS. NEG. NOT GIVEN							POS. NEG. NOT GIVEN						
SIMILAR CONDITIONS							SIMILAR CONDITIONS						
POS. NEG. NOT GIVEN							POS. NEG. NOT GIVEN						
Objective sensory changes							Low-back signs*						
Buttocks	5	61	2	3	33	5	Abnormal position	40	36	2	20	21	0
Anal region	2	64	2	2	34	4	Muscular spasticity	45	28	5	22	19	0
Thigh	16	30	2	7	29	5	Change in lumbar curve	33	41	4	19	21	1
Lower leg	27	39	2	11	25	5	Limitation of motion	47	28	3	21	20	0
Foot	22	44	2	9	26	6	No low-back signs	15	0	0	14	0	0
Great toe	7	59	2	2	33	6	No note	0	0	1	0	0	0
Little toes	7	59	2	5	30	6	Sciatic-nerve stretch tests						
Sciatic nerve	2	0	0	0	0	0	Lasègue	22	10	46	6	3	32
Anesthesia, hyper- and hypesthesia in L4 L5 and S1 areas	8	0	0	8	0	0	Straight-leg raising	51	9	18	20	8	13
None	28	0	2	17	0	5	Tests causing increased intracranial pressure						
Objective motor signs							Coughing	39	6	32	11	14	16
Weakness of legs	25	53	0	13	28	0	Compression of jugular vein	2	0	76	0	0	41
Paralysis of legs	0	78	0	5	33	1	Local low-back, lumbosacral or sacroiliac tenderness						
None of either	0	53	0	0	27	0	41	20	17	20	20	1	
Atrophy of legs	10	68	0	2	39	0	Visceral disturbances						
Babinski sign	0	78	0	2	39	0	Bladder difficulty	3	75	0	4	37	0
Reflexes*							Bowel difficulty	0	78	0	4	37	0
Knee jerk	4	74	0	9	32	0	Both bladder and bowel difficulty	0	78	0	4	37	0
Ankle jerk	33	44	1	15	26	0							
Others	0	77	1	0	41	0							

\*Under reflexes, "positive" indicates an abnormal reflex, "negative" a normal one.

to be significant. Attempts to be too meticulous and to ascribe too great a significance to variations that arise primarily out of the examiner's desire to bolster a preconceived diagnosis may be a source of error. This is not without importance, because there is no doubt that the majority of these patients first

orthopedic surgeon will measure the amount of straight-leg raising in degrees, the more usual interpretation is covered by the terms "present" and "absent." This more liberal and possibly less exact method of listing the results of these tests is more suited to the present knowledge of the condi-

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	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
Less than 1 wk.	0	0	0	0	1	2	2	5
Less than 2 mo.	4	5	22	28	4	10	11	27
Less than 7 mo.	27	35	64	82	10	24	23	56
Less than 1 yr.	39	50	72	92	17	41	27	66
Less than 2 yr.	45	58	78	100	20	49	31	76
Less than 5 yr.	54	69	—	—	31	76	36	88
Less than 10 yr.	63	81	—	—	34	83	—	—
10 yr.	3	—	—	—	—	—	—	—
12 yr.	3	—	—	—	—	—	—	—
13 yr.	—	—	—	—	2	—	—	—
15 yr.	2	—	—	—	1	—	—	—
17 yr.	1	—	—	—	—	—	—	—
22 yr.	1	—	—	—	—	—	—	—
23 yr.	1	—	—	—	—	—	—	—
24 yr.	—	—	—	—	1	—	—	—
26 yr.	1	—	—	—	—	—	—	—
No pain	—	—	—	—	1	—	1	—
Not given	3	—	—	—	2	—	4	—
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			Ankle	15	9
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significance, positive tests being considered by many physicians as practically pathognomonic of rupture of a disk. The figures shown here do not bear this out (Table 6). Whereas 85 per cent of the patients with herniations had a positive straight-leg-raising reaction, 71 per cent of the other series had the same sign. Even if the percentages are figured on the basis of either or both tests' being positive, the comparative figures are still 86 and 70 per cent.

conditions. The numbers are too small to permit any conclusions to be drawn in regard to the jugular-compression test, but there is no doubt that it, too, would show similar results. Neither test helps to differentiate a herniation from a tumor of this region. In this instance my figures are in accord with the statements made by Bradford and Spurling.

*Objective motor signs.* Weakness of the legs occurred in 32 per cent of the cases in each series,

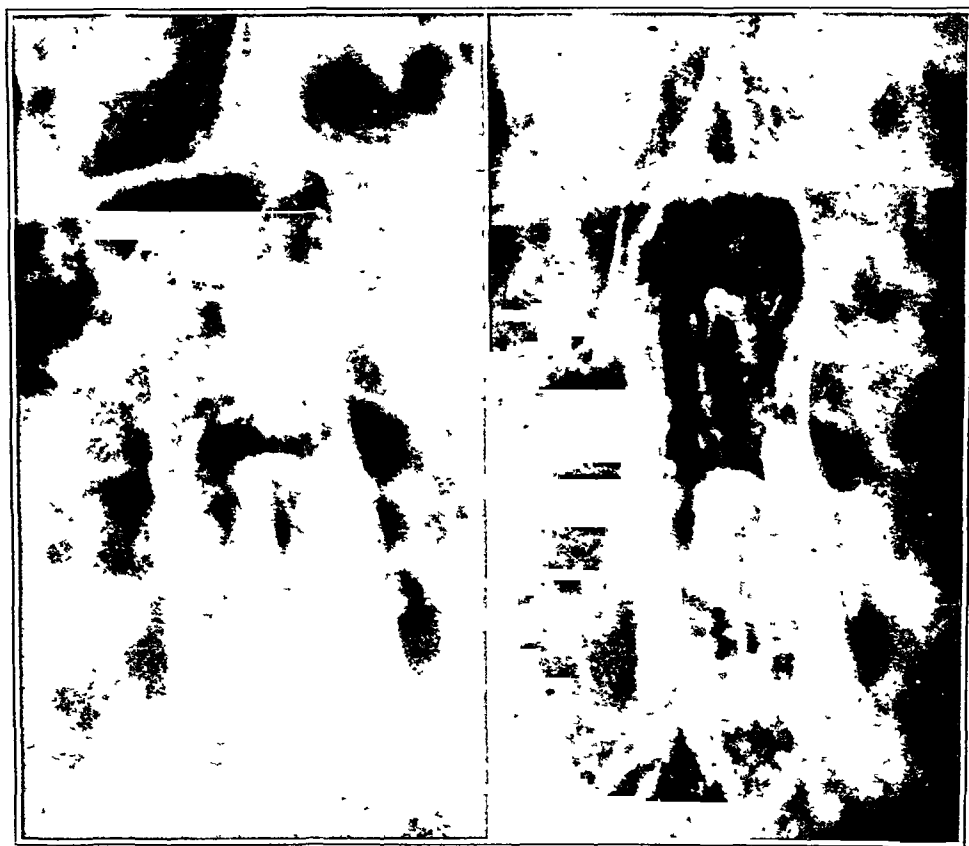


FIGURE 2. *Residual Lipiodol, Injected Elsewhere, before (left) and after (right) Attempts at Removal. This patient had symptoms because of root compression by encysted globules of lipiodol. This was verified by operation.*

From my experience it appears that a positive straight-leg-raising or Lasègue test, whether considered separately or together, only indicates some trouble with the lumbosacral roots or the cauda equina. This trouble may vary from a congenital defect of the spine through a postoperative scar compression of one or more nerve roots to a posterior herniation of a lumbar disk. Doubtless other conditions could be included.

*Tests producing temporary increase of intracranial pressure.* The only significant figures in this regard are those of the cough test (Table 6). Just as in the history, this test is of considerable differential diagnostic import. Although it was positive in 86 per cent of the proved herniation series, there was a similar finding in only 44 per cent of the similar

whereas paralysis was present so infrequently as to be of no significance (Table 6). There was complete absence of both weakness and paralysis in the same percentage of each group. Atrophy was about three times as frequent in the proved herniation series as in the other series, and a Babinski toe response was present in only 2 cases of the second series. If leg atrophy is present in a patient suspected of having a herniated lumbar disk, the chances based on this finding only are three to one in favor of this diagnosis.

*Tendon reflexes.* Great diagnostic and localizing importance has been attached to the absence of an ankle jerk as a sign of herniation of a lumbar disk. My figures show that in patients with proved herniation it is slightly more usual to find the ankle jerks

tion in question. Attempts to be more accurate are analogous to figuring percentages in groups of two-digit numbers to six decimal places; the one is no more diagnostically significant than the other is mathematically so. It is for this reason that in this study the sciatic-nerve stretch tests, the objective sensory changes and other signs, the reflex response and similar reactions are noted only as being present or absent or normal or abnormal.

importance in differentiating a herniation from similar conditions. The figures in the present series support these contentions feebly if at all (Table 6). In particular it should be noted that exclusive of local tenderness no back signs were demonstrable in one fifth of the proved herniations and in one third of the similar conditions. Local tenderness was present in half of the latter as opposed to slightly less than two thirds of the former. As differentially



FIGURE 1. Positive Anteroposterior and Lateral Roentgenograms after Lipiodol Injection.

*Low-back signs.* Spasticity of the lumbar muscles with obliteration or alteration of the lumbar curve and reproduction or accentuation of pain by pressure

diagnostic signs they had no significant value in this series.

*Straight-leg raising and the Lasègue tests.* These

TABLE 7. Data on Objective Findings in Cases of Proved Herniation.

DISK LEVEL AND NUMBER OF CASES	NO OF CASES	NO OBJECTIVE SENSORY CHANGES	SCIATIC NERVE STRETCH TESTS												REFLEX CHANGES						OBJECTIVE MOTOR CHANGES					
			LASEGUE TEST				STRAIGHT LEG-RAISING TEST				BOTH TOGETHER				KNEE JERKS		ANKLE JERKS		OTHER RE-FLEXES		WEAKNESS		PARALYSIS		ATROPHY	
			Pos	Neg	N	G	Pos	Neg	N	G	Pos	Neg	N	G	Pre	Abs	Pre	Abs	Pre	Abs	Pre	Abs	Pre	Abs	Pre	Abs
Third lumbar	4	3(75%)																								
Fourth lumbar	38	15(39%)	13	6	19	21	6	11	8	5	6	37	1 (3%)	26	12 (32%)	38	0	12 (32%)	26	0	38	7 (18%)	31			
Fifth lumbar	32	9(30%)	9	3	20	24	4	4	7	3	4	30	2 (6%)	16	16 (50%)	32	0	10 (31%)	22	0	32	3 (9%)	29			
Fourth and fifth lumbar	3	1(33%)	0	1	2	3	0	0	0	0	0	3	0	2	1(33%)	3	0	0	3	0	3	0	3			
Fourth or fifth lumbar	1	1(100%)	0	0	1	0	0	1	0	0	1	1	0	1	0	1	0	0	1	0	1	0	1			
Totals	78	30	22	10	46	51	10	17	15	8	12	73	5	47	31	78	0	24	54	0	78	10	69			

Abbreviations "Pos" = positive, "Neg" = negative, "N G" = not given, "Pre" = present, and "Abs" = absent

lateral to the spinous processes is, according to Bradford and Spurling,<sup>10</sup> of particular diagnostic

tests, particularly the former. are generally considered to have a considerable differential diagnostic

fourth or the lumbosacral disk that had been ruptured. The number of patients with sensory loss in the great or other toes also seems significant from this point of view. Of the 7 patients with involvement of the great toe, 4 showed rupture of the fourth disk and 3 rupture of the lumbosacral disk. Of the patients with involvement of the other toes, 2 had a rupture of the fourth disk, 4 had a rupture of the fifth disk, and 1 had a rupture of the third disk. Loss of the ankle jerk was present in half of the lumbosacral ruptures but in only one third of the fourth-disk ruptures. Weakness was present

contradictory, however, when used to differentiate ruptures of the fourth and fifth disks. If the objective sensory changes are in the lower leg or foot, this also increases the chances of a herniation. Absence of any objective sensory changes does not militate against this diagnosis. Spasm of the back muscles, abnormal postures, changes in the lumbar curve, loss or diminution of back motion, local tenderness anywhere in the lumbosacral area and a positive straight-leg-raising or Lasègue test are no more characteristic or diagnostic of a posterior herniation of a lumbar disk than they are of any



FIGURE 4. *The Normal Lumbosacral Subarachnoid Space Outlined by Sfiotan. The droplets are from a previous Lipiodol injection done elsewhere and remaining after removal of the bulk of the oil.*

to an equal degree at both levels, but atrophy was twice as frequent with rupture of the higher of these disks. There was no significant difference between the levels in the rate of occurrence of either the positive Lasègue or the positive straight-leg-raising test. On the basis of this series the only objective test with any significant localizing value regarding the level of rupture is absence of the ankle jerk on the affected leg. The presence of atrophy may be of some localizing value.

It seems only reasonable to conclude from these figures that a patient who has an onset of sciatic pain or who has that pain increased if it is already present, by any test that increases the intracranial pressure has a slightly better than two to one chance of having a herniated disk as the cause of his pain if he has no intraspinal tumor. If he has an absent ankle jerk and atrophy of some of the muscles of the affected leg, his chance of having a herniation is slightly increased. These two tests are mutually

other of a variety of low-back, lumbosacral-root or cauda-equina diseases or injuries.

*Cerebrospinal-fluid data.* As has been repeatedly emphasized, alterations in the pressure, dynamics and total protein content of the cerebrospinal fluid below the level of a herniated lumbar disk are no more characteristic of this condition than they are of any other condition that interferes with the circulation of the fluid. Love<sup>11</sup> differentiates herniations and tumors on the basis of total protein content, claiming that values over 100 mg. per 100 cc. usually mean a neoplasm. The present series of conditions similar to herniated disk contained only 1 patient with a tumor. This tumor did not cause a block and the protein content was below 50 mg. It is impossible to draw any conclusions about this particular differential diagnostic problem. I am in complete agreement with Love, however, on the basis of other experience that in "unexplained intractable root pain and in almost every

normal than it is to find them absent in either leg (Table 6). Reference to Table 7 demonstrates that in the proved herniation series its presence and absence were of equally little value in helping to determine which if any disk was ruptured. There was an occasional absent knee jerk in both series, but the figures are too few to justify any conclusions.

*Objective sensory changes.* Just as with the subjective sensory symptoms, the most frequent site for objective sensory changes in proved herniations was in the lower leg, with the foot second (Table 6). This holds true also for the other series, although the preponderance is not so great. The absence of

herniations and in 47 per cent of the similar conditions there was no demonstrable sensory loss of any type in the lower extremities. This does not agree with Bradford and Spurling's<sup>10</sup> statement that 75 per cent of patients with herniations have a demonstrable hypesthesia, but is more nearly in accord with Love's<sup>11</sup> experience that neurologic signs are usually minimal, with hypesthesia or anesthesia over a small segment of the surface of the skin. The importance of objective sensory changes is considerably diminished in the light of these figures, whether considered from the point of view of differential diagnosis or from that of localization

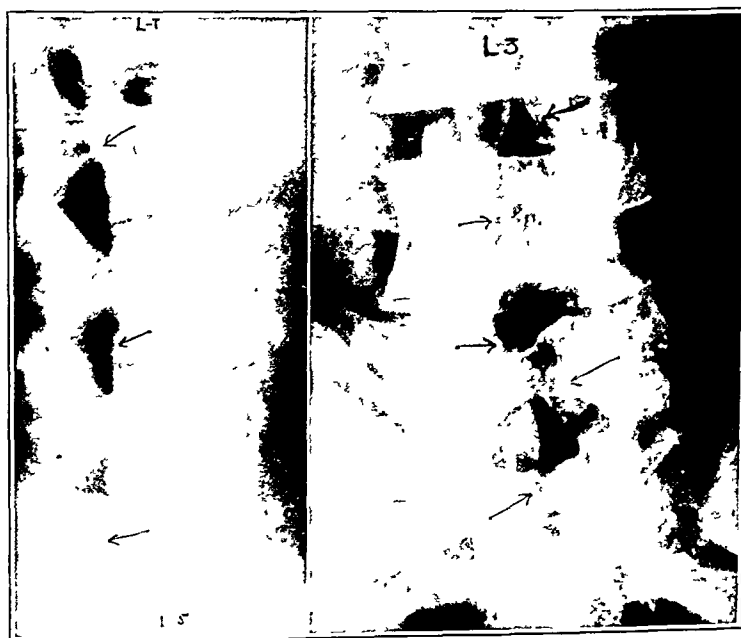


FIGURE 3. Positive Two-Needle Lateral and Anteroposterior Oxygen Myelograms.

positive findings in the toes and particularly in the great toe is especially remarkable. The contrary has been emphasized many times as an important

*Level of herniation.* In Table 7 are listed certain of the above tests with reference to the particular disk that has been ruptured. Mention has already

TABLE 8. Data on Cerebrospinal Fluids and Myelograms.

DATA	NORMAL	PROVED HERNIATIONS HIGH	LOW	NOT GIVEN	NORMAL	SIMILAR CONDITIONS HIGH	LOW	NOT GIVEN
Spinal fluid—								
Pressure	31	4	0	10	34	5	1	3
Total protein	21	16	0	8	25	14	0	4
	NONE	PARTIAL	COMPLETE		NONE	PARTIAL	COMPLETE	
Dynamic block	29	6	0	10	27	8	2	4
	NEGATIVE		POSITIVE		NEGATIVE		POSITIVE	
Serologic reaction	13		0	32	16		0	25
				QUESTIONABLE				QUESTIONABLE
Myelograms								
Lipiodol	0		9	0	0		5	0
One-needle air	0		9	0	1		1	0
Two-needle air	9		22	6	10		10	2
20% Skiodan	0		17	1	5		9	1

differential diagnostic finding, but such a conclusion is not justified by these figures. Most important of all is the fact that in 37 per cent of the proved

been made of the high percentage of patients who showed no loss of sensation. This finding occurred at approximately the same rate whether it was the

needle technic as a contrast medium (Table 8). Until the present manpower shortage affected the supply of skilled x-ray technicians and dark-room workers a fairly satisfactory level of accuracy could be maintained. This was never considered an ideal medium, however, and in the last two years or more it has hardly met minimal requirements. As will be seen from Table 8 about 30 per cent of the examinations were either wrong or not usable for diagnostic purposes. About one and a half years ago, my then resident, Dr. Philip R. Vogel, suggested the use of Skiodan intrathecally as a contrast medium. Before leaving for service in the Army he had completed sufficient preliminary work to demonstrate that a 20 per cent solution of Skiodan could be used in this way with safety and with an

publication. On the evidence collected so far it appears to me and my co-workers that a 20 per cent solution of Skiodan satisfies all the requirements postulated above as necessary to justify the routine use of a contrast medium in the diagnosis of posterior herniation of the lumbar disks. Even were this not so, however, such diagnoses can usually be made with the aid of one of the less satisfactory mediums, and a diagnosis without that aid does not give the patient the full benefit of the surgeon's knowledge and diagnostic opportunities.

#### CONCLUSIONS

A clinical history and examination that even include a study of the cerebrospinal fluid are not enough to justify an indisputable diagnosis of pos-

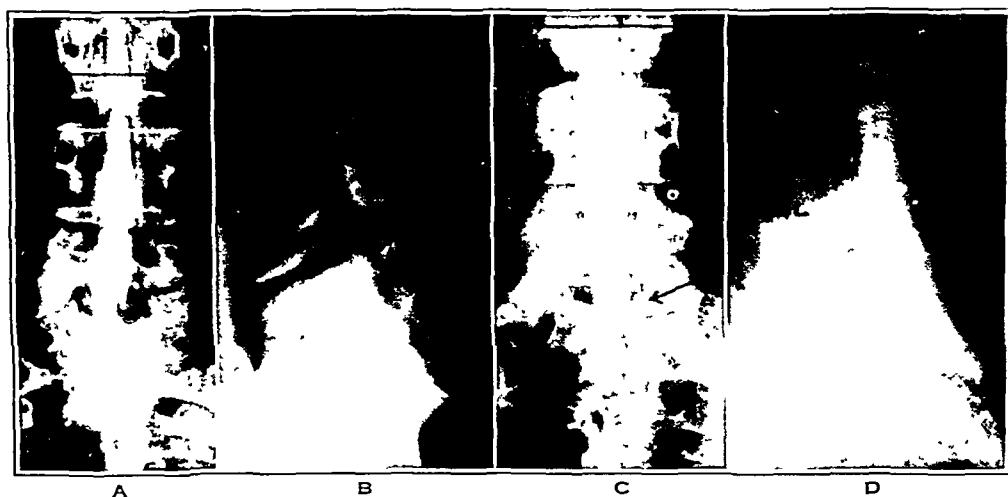


FIGURE 6. Positive Skiodan Myelograms.

*A and B are anteroposterior and lateral views showing a typical deformity at the level of the fifth lumbar intervertebral disk. C and D are anteroposterior and lateral views of the same patient eight months after removal of the disk. There was a compression radiculitis caused by postoperative scarring, with recurrence of the original symptoms; this was verified by operation.*

inconsequential amount of meningeal irritation. provided spinal analgesia — not anesthesia — was first produced (Fig. 4). The injected material was completely absorbed in two hours, and the contrast obtained was as good as or better than that obtained by lipiodol. The use of a fluoroscope was not necessary. Since the technic required making the test with the patient's head elevated, it was thought that the chance of demonstrating borderline herniations was better than with any other method. Individual fibers of the cauda were outlined and the subarachnoid root sleeves were constantly visualized around every root (Fig. 5). Lateral views were equally satisfactory (Fig. 6). The clinical work was then stopped until animal experimentation could verify the safety of the material. This has now been done and recently further more exact and more detailed clinical tests have been carried out as well. An extended report of this work, including a description of the method, will shortly be submitted for

terior herniation of a lumbar disk. An unequivocal recommendation of surgery as a method of treatment is equally unjustifiable under such circumstances. If, however, one can demonstrate a sensory deficit that corresponds to the peripheral distribution of a low lumbar or upper sacral root, together with atrophy and loss of ankle jerk in the same leg, a diagnosis of irritation or compression of this particular root is justified.

If in addition there is a history of intermittent attacks of pain in the back with radiation to any part of the leg, especially to the lower leg, which is associated with initiation or increase of the typical pain by coughing, sneezing or straining, or by back motion or lifting, and if these attacks started after a back injury, back strain, lifting strain or fall, a posterior herniation of either the fourth lumbar or lumbosacral disk must be seriously considered as a cause of the radiculitis. This cannot be regarded as anything approaching a certainty, however, unless



case in which protruded intervertebral disk is suspected diagnostic lumbar puncture should be performed." Insofar as my figures go, the cerebrospinal-fluid pressure, dynamics and total protein (Table 8) were of no help in making a differential diagnosis of posterior herniation of a lumbar disk.

*Myelography.* Almost everyone concerned with the problem of diagnosing and treating posterior herniations of the lumbar disk admits that visualization of the lumbar and sacral subarachnoid space

to be removed by a second procedure, which, although done easily by some, is of some magnitude in the hands of most surgeons (Fig. 2). Pantopaque, the use of which has until recently been limited almost entirely to the medical departments of the Army and Navy, is the next best medium, but except that it is much less irritating and does not have to be removed, it has the same disadvantages that lipiodol has. The use of oxygen and air presents considerable technical x-ray difficulty, and the



FIGURE 5. *Positive Lateral and Anteroposterior Skiogram Myelograms that Show Filling of the Subarachnoid Sleeves Around the Roots.*

is a highly desirable diagnostic prerequisite. Most of this group would also agree that it is an essential if it can be done easily, comfortably and safely and if the degree of accuracy approaches perfection. One has only to refer to the long-continued use of admittedly unsatisfactory mediums and the number and persistence of the attempts that have been made to find a satisfactory one to verify this impression. Of the media commonly in use, lipiodol certainly affords the best contrasts (Fig. 1). It is an oily solution, however, and as such may lead to false positives through partial emulsification when mixed with the watery cerebrospinal fluid. Examinations made with it have to be done with the aid of a fluoroscope and by a roentgenologist capable of operating this apparatus. It is irritating and has

percentage of unsatisfactory films and wrong diagnoses is admittedly too high. In addition, the examination must be made with the feet higher than the head, and this position must be maintained for twenty-four hours or longer if post-lumbar puncture headache, which may be extremely severe, is to be even partly avoided. To be sure, a fluoroscope is not required, the gas absorbs itself, and there is little or no meningeal irritation. Two lumbar punctures are required to get the greatest number of satisfactory visualizations (Fig. 3).<sup>12</sup> Thorotrast and iodine in poppyseed oil have also been used, but the former is considered too dangerous and the latter does not provide adequate contrast, so that their use has been abandoned.

For the most part we have used air by a two-

more particularly of the Rolandic area, produced by histamine effect, is the underlying cause."

The idea that aldehydes and peroxides present as impurities in ether may cause convulsions, held by earlier writers, is now known to be untrue.<sup>9</sup> Further, this contention cannot hold when convulsions develop with the use of agents other than ether.

Many other etiologic factors have been proposed, often without any sound foundation. Excess and deficiency of carbon dioxide have been suggested, as well as conditions vaguely described as irritability of the nervous system, overbreathing, latent tendency to fits, sex susceptibility and others not worth mentioning. Even a neurotoxin produced by streptococci has been suggested.<sup>10</sup> Certain of the above may possibly influence the development of a convulsion, especially the carbon dioxide content of the blood, but there has not been demonstrated a constant cause-and-effect relation in every case.

There are a few factors, however, that seem to be present in many cases, although not all. These, appearing as a definite undercurrent in most discussions of the problem, are youth, the presence of sepsis with fever, and hot, humid external surroundings. Some have claimed that these convulsions are due to heat stroke. According to Payne,<sup>11</sup> however, edema and hyperemia of the brain, with nerve-cell degeneration as described in heat stroke, have not been observed in anesthetic convulsions. In view of the possibility that heat is a factor, other writers have suggested that the pre-operative administration of atropine is deleterious, the drug acting by inhibiting heat loss. Regarding high wet-bulb temperature, it is interesting to note Brennan's<sup>12</sup> statement to the effect that no convulsion occurred in any of five busy theaters after they had been air conditioned six years previously.

These convulsions can appear at any time, and although several authorities have stressed the importance of neurogenic stimuli,<sup>12</sup> with the convulsion commencing at the moment the peritoneum is grasped in forceps or incised, or as soon as there is traction on the viscera, several cases have commenced after the completion of the surgical procedure and the discontinuance of the anesthetic.

Whereas it is well to be aware of the possibly deleterious factors of youth, heat and sepsis, it must be admitted that the etiology of anesthetic convulsions is quite unknown, that their onset cannot be predicted in any case and that the practical problem is what to do about them.

The mortality rate is 20 to 25 per cent. Death may occur at any time. One of Tye's patients<sup>13</sup> lived for twenty-nine days in a state of decerebrate rigidity without regaining consciousness. That one can survive a violent convulsion has been shown many times, as is illustrated in the case reported below.

The subject of treatment is also somewhat confused. For example, some have claimed to have effected cessation of the convulsion merely by raising the head, and others by elevating the feet. Whereas most writers state that withdrawal of the anesthetic is imperative, Tye<sup>13</sup> believes that deeper anesthesia is needed. My opinion in the matter is the same, but I should accomplish this end by discontinuing the inhalation anesthetic and substituting one of the intravenous barbiturates, either 5 cc. or more of a 2.5 per cent solution of Pentothal Sodium, as recommended by Lundy,<sup>14</sup> or 0.5 gm. of sodium amytal. Should these not be immediately available, intravenous magnesium sulfate may be given, since magnesium is not only a depressant of the central nervous system but also blocks the nervous stimulation of voluntary muscles.<sup>7</sup> In the event of an overdose of magnesium, it is to be remembered that respiratory failure from such a cause is best combated not by the usual respiratory stimulants but by intravenous calcium. Concomitantly intratracheal oxygen should be administered. Of course, the operation should be completed as quickly as possible. For hyperthermia, ice bags placed on the body assist in lowering the temperature. If severe hypertension develops, phlebotomy and drainage of spinal fluid are advisable.

#### CASE REPORT

R. W., a well-developed and nourished 17-year-old boy, entered the Mercy Hospital on March 18, 1944, complaining of abdominal pain for 24 hours. From the history and physical examination, together with a white-cell count of 22,500 and a rectal temperature of 99.8°F., a diagnosis of acute appendicitis was made. The patient was given 11 mg. of morphine sulfate and 0.4 mg. of atropine sulfate. Forty-five minutes later anesthesia with nitrous oxide, oxygen and ether was started.

Whereas the patient came to the operating room feeling apprehensive, the induction was fairly smooth, and at the beginning of the operation 15 minutes later the patient was well relaxed and showed the ordinary signs of anesthesia, with good color, the pulse, respirations and blood pressure (150/70) being within normal limits. Through a McBurney incision a gangrenous retrocecal appendix was found and freed with some difficulty, during which there was considerable tugging on the cecum. As the appendix was freed, and just prior to removal, the anesthetist noticed twitchings of the neck muscles, and 30 seconds later these became generalized. The convulsion lasted for 35 minutes. As soon as the twitching became generalized and violent, the surgeon who was assisting left the operative field to deal with the emergency, while with the help of the scrub nurse I proceeded with the removal of the appendix and the wound closure, this being accomplished with considerable difficulty, since the patient was making violent convulsive movements.

The pupils were widely dilated during the convulsive seizure. The blood pressure during most of the time was too high to be recorded. The highest systolic record was 280, and the diastolic pressure at that time was 150. During this interval the pulse rose to 160 to 180 and the rectal temperature rapidly rose to 104°F. As soon as the convulsion started oxygen was given under pressure and was continued until the attack ceased. A phlebotomy was performed, 600 cc. of blood being removed, and then 50 cc. of 50 per cent glucose solution and 20 cc. of 10 per cent magnesium sulfate were administered intravenously. As soon as the wound was closed, the patient was rolled on his side and 15 cc. of spinal fluid was removed; it was not under

confirmed by other and more accurate data. Additional symptoms and signs, whether present or absent, neither strengthen nor weaken this possibility. A positive straight-leg-raising or Lasègue test, limitation or loss of back motion, a change in the lumbar curve, spasm of the erector spinae muscles and local tenderness in the lumbosacral area indicate only that the patient has some trouble with his low back, lumbosacral roots or cauda equina and neither confirm nor deny the diagnosis of a herniation.

A history and examination such as given above, if accompanied by a partial or complete dynamic block or an increase in the total protein of a sample of cerebrospinal fluid properly collected from below the level of the block, or both of these, justify a diagnosis of irritation or compression of any part or all the cauda equina and a probable diagnosis of either an intraspinal tumor or a midline posterior herniation of a lumbar disk. Final differentiation must at least await myelography, and in many cases operation.

The level of herniation, if one is present, is usually not determinable on the basis of pure clinical data, and it is entirely out of the question to diagnose and to localize multiple herniations without adequate actual preoperative visualization of the lower subarachnoid space.

Certain diagnosis, both concerning the presence of a herniation or herniations and concerning the

level, depends on adequate visualization of the lumbosacral subarachnoid space by some opaque contrast medium. So far, a 20 per cent solution of Skiodan has proved satisfactory for this purpose.

Clinical examinations lay the groundwork for suspecting the presence of a posterior herniation of a lumbar disk. Contrast myelography proves or disproves this suspicion, determines the level of the herniation, and leads to a minimal amount of surgery, should this be indicated.

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## CONVULSIONS DURING GENERAL ANESTHESIA

EDMUND E. SIMPSON, M.D.

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THE development of a convulsion in a patient while under general anesthesia is indeed a harrowing experience. Approximately 200 cases have been reported since 1927, but before that time, for some unexplained reason, there appears to have been little on the subject in the literature. Apparently the earliest report is that of Patch.<sup>1</sup> Later, Taylor<sup>2</sup> recounted a case of convulsions under ether anesthesia occurring in the late eighteen-forties. It was not until 1927, however, that general interest became manifested in the condition following publication of the papers of Pinson,<sup>3</sup> who attributed the attacks to excessive concentrations of carbon dioxide, and of Wilson,<sup>4</sup> who believed that impurities in the ether were responsible.

The older term "ether convulsions" is inappropriate since these attacks have been described as occurring as well under anesthesia employing nitrous oxide and oxygen, chloroform, vinethene, ethylene and cyclopropane. The attack itself almost

uniformly commences with twitchings about the eyelids or face or neck muscles and rapidly spreads to the entire body, with generalized and violent clonic convulsive movements. There have been no reports of one development under these circumstances, namely, that of extreme hypertension, to be described below.

A great deal has been written in an attempt to explain the cause of this phenomenon. Lund<sup>5</sup> listed thirty-three possible causes mentioned in the literature, none of these being entirely satisfactory. In fact, there is nothing but contradiction throughout the literature on the etiology of this condition. One of its curious features, as pointed out by Durans,<sup>6</sup> is that whereas a few authors have described a series of several cases, many surgeons and anesthesiologists have never seen a single case.

Many consider anoxemia to be the cause, but Goodman and Gilman<sup>7</sup> deny this, stating that the attack may occur in the presence of a high oxygen tension in the blood. Newman<sup>8</sup> cites an author who stated, "Increased vascularity of the cortex cerebri

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more particularly of the Rolandic area, produced by histamine effect, is the underlying cause."

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increased pressure. Sodium amytal was called for, but was not available.

At the end of the convulsion, ice bags were applied and the temperature started to drop, as did the pulse and blood pressure. The last blood pressure reading in the operating room, 20 minutes after the convulsion ceased, was 165/85. The blood pressure continued to drop, and 1 hour later it was 90/28. At that time 250 cc of plasma and 5 cc of coramine were given. The blood pressure rose rapidly to within normal limits, and thereafter the patient continued to show steady improvement. He regained consciousness only slightly more slowly than one would expect of a patient who had received a general anesthetic, and by morning showed no neurologic changes and felt well. The only complication was a small wound abscess, which healed rapidly. The last blood pressure reading, taken on the 16th postoperative day, was 120/78. Two months postoperatively the patient was back at work as a surveyor feeling quite well.

The anesthetic consisted of a small amount of nitrous oxide and about 45 cc of ether, which seemed to be tolerated well. The spinal fluid showed a weakly positive Pandy reaction, a protein level of 30 mg per 100 cc, a normal cell count, a negative Wassermann reaction and a colloidal gold curve of 2211100000.

It was impossible to determine a cause-and-effect relation in this case. There is no explanation for the rise in the blood pressure to so high a level, much higher than that seen after violent physical exertion or even after therapeutic convulsions.<sup>15</sup> Probably the duration of the convulsion had a great deal to do with the high readings. Perhaps the blood pressure mounts to high levels in such cases and has not happened to be recorded.

As for the increase in body temperature, this could have come about as the result of the muscular exertion. Perhaps, however, the temperature rose during the early part of the operation, unknown to us, and after reaching a certain level contributed to the development of the convulsion. In any event, this case illustrates how complete recovery may follow such a violent episode. It is impossible to state to what extent the intravenous glucose and magnesium sulfate assisted in recovery.

For an extensive bibliography on the subject of anesthetic convulsions the reader should consult the article by Ray and Marshall.<sup>9</sup>

### SUMMARY

Convulsions occurring during general anesthesia are not rare, and may occur with the use of any general inhalation anesthetic.

The etiology is unknown, although youth, the presence of fever and hot, humid external surroundings may be important factors.

The mortality rate is 20 to 25 per cent.

Treatment must be immediate and energetic, the use of oxygen and intravenous barbiturates being particularly important.

That one can survive a violent convulsion an extreme hypertension without aftereffects is shown by the case reported.

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## GIANT CALCULUS OF THE APPENDIX

## Report of a Case

LEWIS S. PILCHER, M.D.\*

NEWTON, MASSACHUSETTS

THERE are few reported cases in the medical literature of the formation of large calculi in the appendix. The two largest appendiceal calculi known are the one reported by Packard<sup>1</sup> in



FIGURE 1. Roentgenogram of Abdomen, with a Catheter in the Right Ureter, Showing the Large Calcified Mass in the Right Pelvis.

1921, measuring 1.0 by 2.0 by 4.0 cm., and the one reported by Bunch and Adcock<sup>2</sup> in 1939, measuring 2.75 cm. in each direction. The calculus in the case reported here also measured 2.75 cm. in diameter. So far as can be determined, these 3 cases are the only ones of true calculi of such large size found in the appendix.

The mechanism of calculus formation in the appendix is probably similar to that in the gall bladder, with chronic partial obstruction of the appendix,

stagnation of the retained appendiceal secretions and gradual formation and calcification of the mass centering around a dried-out fecal concretion. The rarity of fully formed calculi in the appendix may be due to the fact that in most cases the irritation and obstruction produced by the original fecal concretion set up a circulatory disturbance in the appendix, resulting in strangulation and gangrene at an early stage before a calculus has a chance to form.

The history of the case reported below was particularly interesting because there were so few early symptoms in spite of the fact that the calculus must have been forming in the appendix for a long period of time.

## CASE REPORT

H. S., a 34-year-old man, entered the Newton Hospital complaining of pain in the lower back and the right lower quadrant of the abdomen for 2 weeks. The pain in the back was dull and steady, and on subsequent questioning the patient admitted that he had had some pain in that region for a long time, but this was mild and was always attributed to fatigue. The pain in the abdomen, which was what brought him to the hospital, was intermittent, with recurrent, severe, colicky exacerbations. Between the attacks of colic the pain was dull and constant. During the 2 weeks of acute symptoms, there were considerable anorexia and some nausea, but no acute vomiting.

Physical examination on admission revealed slight localized tenderness in the right lower quadrant but no protective spasm. The blood and urine were normal. Since the history was highly suggestive of a right ureteral calculus, cystoscopy and pyelograms were done. These showed a large calcified shadow several centimeters in diameter in the right pelvis adjacent but anterior to the right ureter (Fig. 1). There were several other calcified shadows higher in the right abdomen. A diagnosis was made of calcified, mesenteric lymph nodes. It was believed that the large calcified shadow in the right pelvis was probably also a calcified node, which because of its large size was causing the pain. Operation was therefore advised.

At operation, while waiting for the anesthetist to put the patient in Trendelenburg position, it was decided to look at the appendix. When the appendix was delivered, it was at first thought that it contained a mucocele, and it was difficult to believe there was such a large stone present until the appendix had been opened. The illustrations (Figs. 2, 3 and 4) indicate better than any verbal description the size, character and location of the calculus.

Further exploration of the abdomen showed many large calcified lymph nodes in the mesentery of the cecum and the ileum, as noted by x-ray. No definite relation could be determined between these nodes and the calculus in the appendix, except that it was assumed that the patient had a greater than average tendency to form calcium deposits. Tests of calcium and parathyroid metabolism showed no abnormality. There was no evidence of bony decalcification. There were no renal or gall-bladder calculi.

The most interesting feature of the specimen was that in spite of the marked distention of the appendix by the stone, which was situated at the proximal end of the appendix and completely obstructed it, there was no enlargement of the tip

\*Member of the Surgical Service, Newton Hospital (on leave of absence).

increased pressure. Sodium amytal was called for, but was not available.

At the end of the convulsion, ice bags were applied and the temperature started to drop, as did the pulse and blood pressure. The last blood pressure reading in the operating room, 20 minutes after the convulsion ceased, was 165/85. The blood pressure continued to drop, and 1 hour later it was 90/28. At that time 250 cc. of plasma and 5 cc. of coramine were given. The blood pressure rose rapidly to within normal limits, and thereafter the patient continued to show steady improvement. He regained consciousness only slightly more slowly than one would expect of a patient who had received a general anesthetic, and by morning showed no neurologic changes and felt well. The only complication was a small wound abscess, which healed rapidly. The last blood pressure reading, taken on the 16th postoperative day, was 120/78. Two months postoperatively the patient was back at work as a surveyor feeling quite well.

The anesthetic consisted of a small amount of nitrous oxide and about 45 cc. of ether, which seemed to be tolerated well. The spinal fluid showed a weakly positive Pandy reaction, a protein level of 30 mg. per 100 cc., a normal cell count, a negative Wassermann reaction and a colloidal gold curve of 2211100000.

It was impossible to determine a cause-and-effect relation in this case. There is no explanation for the rise in the blood pressure to so high a level, much higher than that seen after violent physical exertion or even after therapeutic convulsions.<sup>15</sup> Probably the duration of the convulsion had a great deal to do with the high readings. Perhaps the blood pressure mounts to high levels in such cases and has not happened to be recorded.

As for the increase in body temperature, this could have come about as the result of the muscular exertion. Perhaps, however, the temperature rose during the early part of the operation, unknown to us, and after reaching a certain level contributed to the development of the convulsion. In any event, this case illustrates how complete recovery may follow such a violent episode. It is impossible to state to what extent the intravenous glucose and magnesium sulfate assisted in recovery.

For an extensive bibliography on the subject of anesthetic convulsions the reader should consult the article by Ray and Marshall.<sup>9</sup>

### SUMMARY

Convulsions occurring during general anesthesia are not rare, and may occur with the use of any general inhalation anesthetic.

The etiology is unknown, although youth, the presence of fever and hot, humid external surroundings may be important factors.

The mortality rate is 20 to 25 per cent.

Treatment must be immediate and energetic, the use of oxygen and intravenous barbiturates being particularly important.

That one can survive a violent convulsion and extreme hypertension without aftereffects is shown by the case reported.

1127 11th Street

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## SUMMARY

A case of giant calculus of the appendix is reported. It is believed that this is the third calculus of such size in the appendix to be reported in the literature. This calculus was particularly interesting because it was present in the proximal instead of the distal end of the appendix and caused marked

obstruction and distention of the proximal half of the appendix without producing symptoms of appendicitis.

## REFERENCES

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## MEDICAL PROGRESS

## ABDOMINAL SURGERY

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BOSTON

**A**DVANCES in abdominal surgery during the past year have been evaluated. Many of the papers relate to the surgery of trauma and these will not be taken into consideration except when such information may be applicable to problems of civil practice. All reports cannot be included, but many of the timely subjects will be discussed.

## GENERAL CONSIDERATIONS

*Anesthesia*

Arrowood and Foldes<sup>1</sup> have modified Lemmon's<sup>2</sup> method of continuous spinal anesthesia. These authors report the use of a continuous-drop method of maintaining spinal anesthesia in approximately 40 cases. A recent personal communication reveals that over 60 patients have been anesthetized by this technic. Anesthesia is established with the usual 2.5 per cent novocain solution intrathecally, and the needle is left in place and connected to a gravity bottle containing 0.5 per cent novocain solution. Depending on the type of patient and the level of anesthesia desired, from 4 to 8 drops of the weak solution is allowed to enter the spinal canal each minute. No complications arose in any case. The maximum duration of anesthesia was six hours, with a total of 150 cc. of the solution used. Approximately 5 per cent of the cases were considered unsatisfactory due to technical errors. The method is particularly suitable for bad-risk patients and is useful when the operation takes longer than planned. The authors found that unanesthetized patients can be given from 12 to 20 drops of physiologic saline solution a minute without ill effect and without a significant rise in the intraspinal pressure; this is twice the rate of administration required for the anesthetic agent.

I have operated on patients under this type of continuous-drop novocain spinal anesthesia. It has definite advantages over the fractional method in

that there is no interval between doses. Furthermore, with the latter method the surgeon and the anesthetist are often unaware that the anesthesia has worn off until the patient moves or violently strains or protests. The patient under the new modification remains quiet and comfortable without interruption throughout the procedure.

*Early Postoperative Ambulation*

This method of handling patients will increase in popularity now that the use of nonabsorbable suture material has been found to result in little or no lag period in wound healing.<sup>3</sup> It appears that fine steel wire, nylon, cotton and silk cause so little reaction in sutured tissues that there is little evidence of the so-called "weak stage" of the suture lines that frequently occurs when catgut is used.

Rickles<sup>4</sup> reports the results on 146 patients observed at the Charity Hospital in New Orleans. Ninety-eight patients without peritonitis were allowed to walk on the first postoperative day following celiotomy. Eighty-seven patients who had had appendectomies through transverse incisions were allowed home on the third day, returning on the sixth day for the removal of sutures. Patients with peritonitis and those in whom the drainage of an abscess was necessary were allowed up after the danger from intraperitoneal inflammation had passed. Patients operated on for inguinal hernia were allowed to walk on the first day postoperative, and those with ventral hernia on the second. All wounds were sutured with cotton, and all healed by primary intention. There were no disruptions, and no hernias developed in the scars during one year of follow-up. None of the patients required catheterization, and only 3 needed enemas.

Powers<sup>5</sup> reports on the advantages of early rising in 100 cases. The results were as good as those in a control group so far as wound healing and lack of complications are concerned. There was no decrease in postoperative thrombophlebitis in his ambula-

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of the appendix and none of the usual changes in the distal half of the appendix that are generally

how such marked distention and obstruction of the proximal portion of the appendix could have oc-

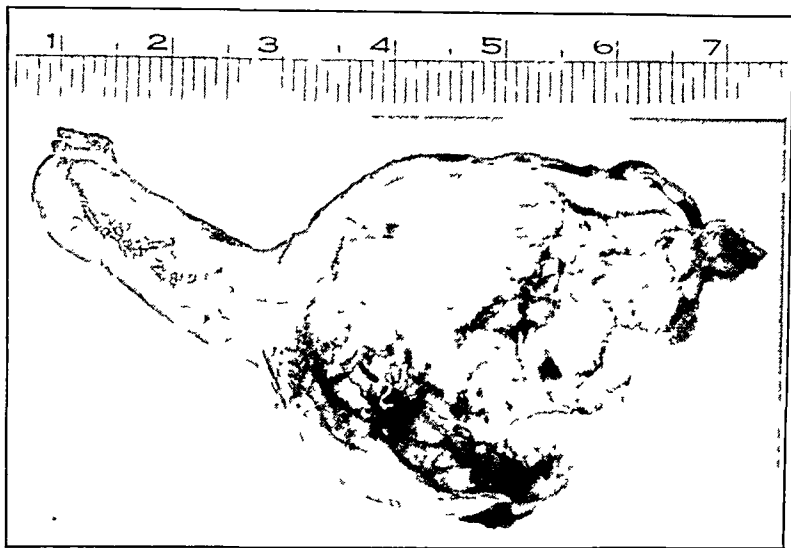


FIGURE 2. Photograph of the Appendix, with the Calculus Distending the Proximal Half.

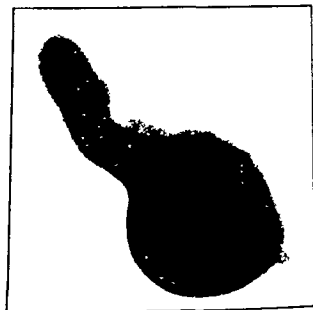


FIGURE 3. Roentgenogram of the Appendix, Showing the Shadow of the Calculus.

supposed to follow obstruction of the proximal portion. This was undoubtedly due to the fact that

curred without producing more pronounced symptoms. The only conclusion of general interest to

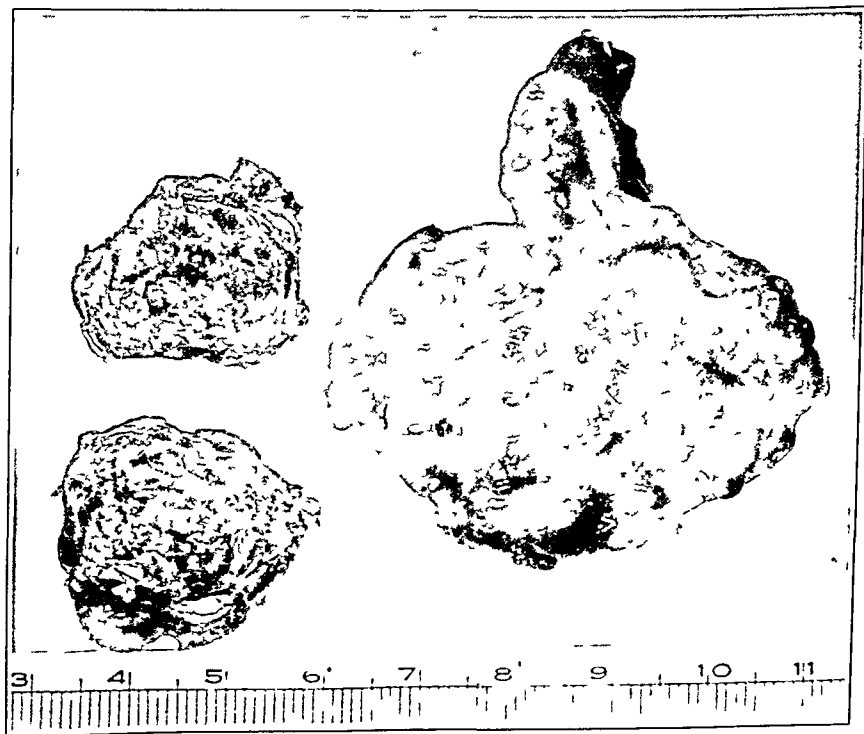


FIGURE 4. Photograph of the Sectioned Stone and Appendix. Note the roughly concentric structure of the stone and the hypertrophied mucosa in the distal half of the appendix.

the calculus enlarged very gradually and caused no acute embarrassment of the circulation of blood or lymph. It is nevertheless difficult to understand

be drawn from this fact is that simple obstruction of the appendix is not by itself the complete answer to the etiology of acute appendicitis.

### *Small-Bowel Obstruction*

Grimson and Hodge<sup>11</sup> corroborate the experience of Folley<sup>12</sup> that Miller-Abbott intubation is often satisfactory as a definitive method of treatment for acute small-bowel obstruction. No time limit need be set for operative interference if the patient does well on the conservative regimen. In 7 cases so treated, 4 were symptom-free from three months to two years without surgery.

It is important to be alert for localized tenderness and maintained or developing leukocytosis, which indicate a gangrenous segment. In my opinion, better results are obtained if surgery is undertaken before gangrenous areas develop or, if already present, before perforation takes place. Equivocal cases should be explored as soon as decompression is under way and the patient's condition is stabilized. The safety of surgery within twenty-four hours after onset, as pointed out by McKittrick and Sarris,<sup>13</sup> cannot be ignored.

### NEOPLASMS OF ABDOMINAL WALL

These are discussed by Pack and Ehrlich<sup>14</sup> in a review of 470 cases treated in the Memorial Hospital, New York City. They classify 391 neoplastic lesions as follows: benign neoplasm, 242; primary malignant neoplasm, 63; metastatic malignant neoplasm, 64; and lymphoma, 22. Of the 79 lesions termed non-neoplastic, 24 were cysts, 31 were inflammatory, and 24 were miscellaneous. The lymphatic spread from all neoplasms of the anterior abdominal wall is similar to that of those starting in the umbilical region. Chronic draining sinuses were a frequent source of cancerous degeneration. They call attention to the so-called "Kangri-burn" epidermoid cancer, which is well known in certain Japanese districts where an earthenware bowl containing burning charcoal is worn next to the skin of the abdominal wall as a method of maintaining warmth. Other apparent sources of epidermoid carcinoma were psoriasis, radiation dermatitis and arsenical dermatitis. Of the 63 primary malignant neoplasms, 25 were carcinoma, 30 sarcoma, and 8 melanoma. They also report 17 cases of desmoid tumors and give an excellent description of this pathologic process. Many of their desmoids had had inadequate removal elsewhere.

### HERNIA

Cutler and Scott<sup>15</sup> report 4 cases of acute small-bowel obstruction from transmesenteric hernia observed at the Children's Hospital in Boston. They have collected 46 additional cases from the literature and state that this type accounts for 11 per cent of all intra-abdominal hernias. The mortality in 50 cases was 38 per cent, although 3 of their 4 patients recovered. The majority of these hernias occurred through developmental defects in the

mesentery, although a few were thought to be due to inflammatory processes and trauma.

Jens<sup>16</sup> reports a study of 100 patients with strangulated femoral hernia who were admitted to one institution in a five-year period. The average age of these patients was sixty-three years. Two thirds were beyond the sixth decade, and three fourths of the patients were women. Forty-two per cent gave no previous history of hernia. Strangulation was ushered in by pain and vomiting of from three hours' to fourteen days' duration in 84 per cent of the cases. Pain was not admitted by 2 of 3 patients having nonviable bowel. Pain was most frequent in the midabdomen (65 per cent), and in all these cases there was omentum or small bowel, or both these structures, in the sac. Pain at the site of hernia was present in 26 cases. It was low abdominal and colicky in nature in 7 per cent, and epigastric in 4 per cent. Tenderness over the site of the hernia was elicited or recorded in only 21 cases. Seven of the entire group were Richter's hernia. Twelve of 20 cases with gangrenous bowel required resection, with a mortality rate of 66 per cent. Two cases with exteriorized gangrenous intestine died. The over-all mortality for the entire series was 14 per cent.

White<sup>17</sup> calls attention to the satisfactory results obtained from simple herniotomy under local novocain anesthesia in the bad-risk patient with strangulated umbilical hernia. Analysis of records of radical repair as an emergency measure revealed a high mortality rate. The dangers of radical cure in this group of patients as an operation of election are also stressed.

Burton<sup>18</sup> emphasizes the better results obtained by autogenous fascial repair in inguinal hernia. In 385 cases repaired by the Gallie method, there were 0.9 per cent recurrences. In 132 cases repaired by the McArthur method, there were 4.5 per cent recurrences. There were 3 cases of testicular atrophy in the larger group. He depicts an ingenious foot sandal, with a canvas strap attached, to maintain the leg in inversion while the fascia lata is being procured.

Ryan<sup>19</sup> corroborates the results obtained by McCloskey and Lehman<sup>20</sup> in the routine use of the McArthur type of repair in inguinal hernia. He advocates cotton sutures to reinforce the wound and uses the Bisgard needle to carry the fascial strip. Ninety-two cases were followed without evidence of recurrence.

A combination of the McArthur and the Halstead I operations, employing fine silk or cotton sutures, has been the minimum standard repair used in adults on the East Surgical Service of the Massachusetts General Hospital for a number of years. It has given extremely low rates of infection and of recurrence in a large group of patients operated on by the resident staff. Alternate cases have been ambulated on the first postoperative day with no

tory cases. He emphasizes the beneficial results of early ambulation and finds no contraindications to its use.

Shorter<sup>6</sup> emphasizes early rehabilitation in abdominal surgery and calls attention to the low incidence of chest complications and the reduction in circulatory disturbances, as well as to the maintenance of muscle and joint tone and the beneficial effect on morale. Patients not suitable for early ambulation were given exercises in bed.

At the Massachusetts General Hospital we have been interested in the good effects of early ambulation, long used in the aged but only in recent years applied to other patients. The danger of wound infection is apparently increased by early rising, but this has not been serious in nature. There appears to be little reduction in thrombosis of the leg veins in ambulatory patients as compared with a control group. So far, there has been no evidence of increased hernia-in-scar, and wound disruption has not occurred. The patient handled in this manner remains in good physical condition and is able to resume his usual activities at an early date.

### *Sulfonamides*

The use of sulfonamides in abdominal surgery is challenged by Rea,<sup>7</sup> who states that a recent review of the literature reveals that many reports are misleading. The experience of the operator using modern methods of preparation, anesthesia and aftercare makes comparative data based on earlier cases open to question. He points out that only alternate cases treated by the same surgeon under the same conditions at the same season of the year with and without sulfonamides would reveal their true value. Experimental work is cited to support the better effect of sulfonamides as a preventive measure to infection rather than a curative one after suppuration has been well established. He was unable to observe that the intraperitoneal use of sulfonamides influences the outcome in suppurative peritonitis of enteric origin in experimental animals, and is of the opinion that pus inactivates the sulfonamide.

It is my opinion that the intravenous use of sulfadiazine is superior in its effect and perhaps safer than the intraperitoneal use of sulfonamides. The former drug can be continued by mouth as soon as adequate fluids can be given by this route. Rare cases in which renal and ureteral crystals are formed must be kept in mind and properly treated.

### *Glove Powder*

Talcum is generally used as a glove powder, but this substance is criticized by Seelig, Verda and Kidd.<sup>8</sup> These authors point out the danger of producing a serious adhesive, granulomatous foreign-body reaction if any talcum powder is allowed to

come in contact with peritoneal surfaces. If too much powder is used in the glove and the finger tip becomes punctured, great damage may be done from a small amount of talcum spilled into the peritoneal cavity. They found after much experimentation that a powder (210 to 270 mesh) of potassium bitartrate (cream of tartar) was harmless in the peritoneal cavity of experimental animals. This material shortened the life of rubber gloves by one half.

In trying this substitute for talcum at the Massachusetts General Hospital, we have found that the glove is often sticky and difficult to get on. It seems necessary to find a better powder than potassium bitartrate before it can be satisfactorily used. Until a suitable material can be found, one can either use wet gloves or reduce the danger to a minimum by using talcum sparingly inside the gloves, and washing the outside after putting them on.

### *Management of Penetrating Wounds*

Zininger<sup>9</sup> gives an excellent outline for the evaluation and management of penetrating wounds of the abdomen. First of all, the degree of shock must be determined, and this combated by plasma followed by blood. Only the patient with obvious continued internal bleeding should be operated on before shock is controlled. The second consideration is the nature of the injury, its extent and the direction of the penetrating missile. This is often best determined by a scout roentgen film if there is no wound of exit. From the location of the foreign body on the film and the point of entry, the structures penetrated can be surmised. The third important observation is whether or not there is evidence of peritoneal irritation. He prefers intratracheal cyclopropane anesthesia and, if the intestine has been penetrated, advises the use of 5 to 10 gm. of sulfanilamide intraperitoneally as well as intravenous sulfadiazine. He is of the opinion that through-and-through closure of the abdominal wall with silver wire is the method of choice in these cases.

Noble<sup>10</sup> proposes an ingenious method of treating old wounds of the small intestine by plication of one loop of gut to its nearest segment. This is carried out through the entire small bowel. He advises hourly doses of Pitressin and claims recovery in 90 per cent of a large series of cases so treated. He believes that local closure of perforations leads to stasis above and between such areas of repair and that the high number of poor results under these circumstances are due to the absorption of toxins from partially obstructed segments of bowel.

One wonders whether this complete plication of the small intestine would be useful in cases of extensive adhesions with repeated episodes of small-bowel obstruction, particularly if the mesentery was such as to lend itself to repeated volvulus.

er tube. Intestinal continuity is re-established by implanting the proximal jejunum end-to-side into the distal limb at a point approximately 18 cm. from the portal fissure. These patients have had no bile leakage at the anastomotic site. There has been less evidence so far of the frequently disabling cholangitis observed after other methods of repair. Theoretically, there should be less chance of cicatricial constriction at the anastomosis and less chance of ascending cholangitis, since the lumen of the gut is large and the peristaltic current is away from the liver ducts. It will require a greater experience and a longer follow-up period to determine the actual advantages of this method, if any.

Best<sup>9</sup> calls attention to the frequency of liver-duct stones that cannot be removed surgically. He states that the incidence of such stones is about 7 per cent of patients with cholelithiasis. Although he fails to discuss the possibility that these stones will spontaneously leave the liver if the papilla of Vater is gradually dilated to a diameter slightly larger than that of the hepatic ducts, he brings out helpful information regarding flushing the biliary system before and after operation. His method is used a few days prior to exploration and about the eighth and fifteenth days postoperatively. The treatment is carried out three days in succession. On the first day, this patient is given 3 tablets of Decholin or Procholin three times a day and at bedtime, 0.6 mg. (1/100 gr.) of nitroglycerin before meals, 30 cc. of pure cream before the evening meal and at bedtime and 8 gm. of magnesium sulfate before breakfast. The second day varies only by substituting 0.6 mg. of atropine sulfate for the nitroglycerin. The third day's regimen is the same as that of the first.

I have found this method of treatment helpful in a few cases of cholangitis following common-duct reconstruction. In one case, it has been continued with more or less regularity three days each week, since symptoms of mild pain, chills, fever and itching recur if the treatment is omitted for any length of time.

Ferguson<sup>31</sup> reports an ingenious method of treating chronic ascites. In a patient requiring frequent paracenteses, one of the two normal kidneys was removed and its pelvis implanted into the peritoneal cavity. This was successful only after the third operation, when the implantation was located behind the lower posterior rectus sheath where it functioned perfectly throughout one year of observation. The two previous attempts at implantation in other locations ceased to function after a while owing to plugging of the ureteral orifice with omentum and so forth. The patient voided the ascitic fluid with the urine secreted by the remaining kidney.

Pickrell and Clay<sup>32</sup> report the successful removal of the left lobe of the liver in 3 patients, one of whom had a primary carcinoma, one a hemangioma, and one a gumma thought at the time of operation to be

a carcinoma. They have collected only 56 cases of liver lobectomy from the literature and state that no other author has reported more than a single case.

## ULCER OF STOMACH AND DUODENUM

Much has been written about the importance of the ulcer problem in military personnel. Tidy<sup>33</sup> makes an exhaustive report on the situation in the British army. Having analyzed 800 army cases, he found that 58 per cent of all patients admitted with dyspepsia were found to have ulcer. He stresses the need for accurate diagnosis and believes that soldiers with ulcer should have duty compatible with a suitable dietary regimen. Those with functional disorders should be diagnosed early and sent to regular duty before they become neurotic about their symptoms. He states that if the diagnosis of ulcer was incorrectly made on a man with a functional disturbance, it became difficult to overcome this error. He claims that there is no evidence to support the theory that ulcer is more liable to develop in soldiers than in civilians. Eighty per cent of all army personnel having ulcer were found to have had symptoms for an average of seven years, dating back into civil life.

This accurately corresponds with the data on this subject reported by Rush<sup>34</sup> regarding American soldiers in the combat zone. He agrees that soldiers with ulcer are not suitable for combat duty. This is in accord with the report by Logan<sup>35</sup> regarding men in the Navy.

Rook<sup>36</sup> studied this situation in the Royal Air Force. He selected 194 cases and followed them for two and a half years. Only half these men were eventually able to do flying duty. The higher the rank, the more the likelihood that the man would be able to carry on. Of the whole group, two thirds are still in service and one third have been invalided. He claims that neither the length of the history nor any of the criteria of diagnosis appear to offer guidance whether or not an airman after treatment for ulcer is likely to withstand service life.

In 200 dyspeptic soldiers, Guyer<sup>37</sup> compares the diagnosis by means of fluoroscopy and gastroscopy. The findings were normal by both methods in about 40 per cent of the cases. Roentgenologic studies were normal in the cases (nearly 31 per cent) found to have gastritis gastroscopically. Duodenal or gastric ulcer was found by one or both methods in only 16.5 per cent of the group studied.

Spicer, Stewart and Winsor<sup>38</sup> report that perforated ulcer increased from approximately 25 to 35 per cent during the London Blitz. This fell to normal or below after the air raids ceased. The authors attempt to show the effect of anxiety on ulcer activity. They fail to take into consideration the physical hardships of air-raid shelters, with the almost certain change in dietary habits.

serious complications and with much less invalidism than that in a control group. The early risers have been kept in the hospital until the tenth post-operative day, whereas those treated for twelve days with recumbency have averaged fifteen days of hospitalization.

### BILIARY SYSTEM

White<sup>21</sup> gives an excellent presentation on the differential diagnosis in jaundice. In 175 cases, the proved error in diagnosis was 8 per cent; half these were due to overlooking small or latent tumors. He states that there is too great a tendency to make a diagnosis of portal cirrhosis in the alcoholic patient when the obstruction is actually due to cancer. Partial obstruction proved to be caused by benign lesions in 91 per cent of the cases, and complete obstruction was due to cancer in 96 per cent. This, I believe, is not the generally accepted rule and probably is the result of including a large number of cases of toxic hepatitis and biliary cirrhosis with those of obstructive jaundice. White believes that hurried exploration is seldom justified and that many of the cases can be correctly diagnosed by sufficient time and study. The easiest cases to diagnose were those with toxic and infectious hepatitis, those with complete external obstruction and those with hemolytic jaundice. Patients with multiple lesions, those who were extremely ill and on whom complete study was not possible and those with tumors of the liver and bile passages offered the greatest diagnostic difficulties. Surgery undertaken on the diagnosis of obstructive jaundice in patients suffering from hepatitis gave a high mortality rate.

Benedict<sup>22</sup> has demonstrated the value of peritoneoscopy and biopsy of the liver for diagnosis in equivocal cases. In most cases, the pathologist can make a definite diagnosis of obstructive jaundice or hepatitis from the biopsy specimen. This method should be used earlier and oftener, since the opportunity for radical cure by the Whipple operation in cancer of the ampulla of Vater or head of the pancreas may be lost if delayed too long.

Truesdell<sup>23</sup> routinely palpated the gall bladder in 500 women undergoing abdominal pelvic surgery and found 50 cases of gallstones. A careful review of the history revealed that only 2 of these patients had had no symptoms referable to the gall bladder. Of these 50 patients, 8 died more or less promptly, 6 received immediate cholecystectomy, 12 sooner or later returned for operation, 12 were lost sight of, and 12 remained under observation.

Robertson and Dochat,<sup>24</sup> in a collective review, have challenged the usually accepted viewpoint that women who have borne children are more apt to have gallstones than are spinsters. They estimated that 79.25 per cent of all women have borne children; this figure is practically identical with the percentage of parous women with gallstones re-

ported by thirty-four authors — 79.6 per cent 11,154 of 14,016. They admit that gallstones are two or three times as common in women as in men but refute the belief that pregnancy plays any part in their development.

Bearse<sup>25</sup> analyzed 253 consecutive persons treated in cases of gallstones. Thirty-nine per cent of his patients had complications from the stones at the time of operation. Twenty-seven per cent had acute inflammation of the gall bladder, including empyema, gangrene and perforation. Twelve per cent had common-duct stones. Four per cent had acute pancreatitis, and 3 patients had carcinoma of the gall bladder. There were 16 postoperative deaths in the series, only 3 of which were attributable to delay in surgical treatment. He deduces that delay may be justifiable in the absence of complications but that when complications are present prompt treatment is imperative.

Cowley and Harkins<sup>26</sup> found only 25 cases of perforation of the gall bladder in 2750 patients with cholecystic disease treated at the Henry Ford Hospital in Detroit in twenty-two years. They admit that the differential diagnosis of acute cholecystitis without and with perforation is difficult and uncertain. They are of the opinion that operation after election between attacks should be stressed rather than early operation after acute symptoms develop.

Finney<sup>27</sup> analyzed all cases of carcinoma of the gall bladder treated at the Union Memorial Hospital in Baltimore and substantiates the general opinion that all these patients had gallstones. He stresses the danger of advising good-risk patients with gallstones against operation of election, even if their symptoms are minimal. The unsatisfactory results of operation after cancer develops strengthen his argument.

Walton,<sup>28</sup> in a fascinating treatise, calls attention to the great importance of careful biliary-tract surgery. Anomalies of the bile ducts and blood supply are far more frequent than usually thought. Injuries due to anomalies or to carelessness often result in fatalities, and when the patient survives, it may be only for a short period of invalidism. He reviews the literature regarding the various methods of establishing continuity between the injured bile duct and the gastrointestinal tract. He reports on his own experience with a method of a valve-like anastomosis between the hepatic duct and the duodenum. As in practically all other such reports, the results leave much to be desired.

I<sup>29</sup> have recently reported the immediate results of re-establishing continuity between the bile duct and the gastrointestinal tract by a new method which was first mentioned in the progress report for 1940. Eight patients have been treated by implantation of the hepatic duct into the distal transected end of the jejunum 30 cm. from the ligament of Treitz. The cut end is inverted and the anastomosis accomplished over a

er tube. Intestinal continuity is re-established by implanting the proximal jejunum end-to-side into the distal limb at a point approximately 18 cm. from the portal fissure. These patients have had no bile leakage at the anastomotic site. There has been less evidence so far of the frequently disabling cholangitis observed after other methods of repair. Theoretically, there should be less chance of cicatricial constriction at the anastomosis and less chance of ascending cholangitis, since the lumen of the gut is large and the peristaltic current is away from the liver ducts. It will require a greater experience and a longer follow-up period to determine the actual advantages of this method, if any.

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#### ULCER OF STOMACH AND DUODENUM

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This accurately corresponds with the data on this subject reported by Rush<sup>34</sup> regarding American soldiers in the combat zone. He agrees that soldiers with ulcer are not suitable for combat duty. This is in accord with the report by Logan<sup>35</sup> regarding men in the Navy.

Rook<sup>36</sup> studied this situation in the Royal Air Force. He selected 194 cases and followed them for two and a half years. Only half these men were eventually able to do flying duty. The higher the rank, the more the likelihood that the man would be able to carry on. Of the whole group, two thirds are still in service and one third have been invalided. He claims that neither the length of the history nor any of the criteria of diagnosis appear to offer guidance whether or not an airman after treatment for ulcer is likely to withstand service life.

In 200 dyspeptic soldiers, Guyer<sup>37</sup> compares the diagnosis by means of fluoroscopy and gastroscopy. The findings were normal by both methods in about 40 per cent of the cases. Roentgenologic studies were normal in the cases (nearly 31 per cent) found to have gastritis gastroscopically. Duodenal or gastric ulcer was found by one or both methods in only 16.5 per cent of the group studied.

Spicer, Stewart and Winsor<sup>38</sup> report that perforated ulcer increased from approximately 25 to 35 per cent during the London Blitz. This fell to normal or below after the air raids ceased. The authors attempt to show the effect of anxiety on ulcer activity. They fail to take into consideration the physical hardships of air-raid shelters, with the almost certain change in dietary habits.

Raw<sup>39</sup> analyzed 1052 cases of perforated ulcer occurring from 1937 to 1941 in England and showed a yearly rise from 181 cases in 1937 to 251 in 1941. The average age of the patients was forty-two years, which was obviously influenced by the younger citizens being in military service. The death rate under the age of forty-two was 7.6 per cent, whereas over forty-two it was 21.3 per cent. He calls attention to the fact that delay in operation was more frequent in women than in men, owing to the fact that in the former the acute onset was incorrectly interpreted as due to gallstone colic. The average delay in the women of this group was eighteen hours, with a shocking mortality rate. The author agrees that the closure should be made as early as possible with minimal surgery and with gentleness but reasonable speed.

Wakeley<sup>40</sup> compares a group of 102 civilians and 103 naval personnel with perforated ulcer. The civilians averaged forty-six years of age, with a mortality rate of 20 per cent, and the naval group averaged thirty-two years of age, with a mortality rate of 8 per cent. He believes that the Royal Navy, having standardized its treatment by immediate gastric suction, early closure and sulfanilamide therapy, may reduce the mortality rate to 1 per cent.

Walters and Butt<sup>41</sup> make a strong plea for radical surgery in the personnel of the United States Navy with duodenal ulcer. They point out that the operative mortality is very low and that 85 per cent of the patients so treated were returned to active duty. A comparable analysis of a much larger group treated medically showed that only 50 per cent were able to return to active duty. These authors believe that many valuable men can be retained in service after proper subtotal gastric resection.

Weinstein et al.<sup>42</sup> have completed some experimental work on animals and operated on 6 patients for ulcer by various incomplete interruptions of the vagus nerves. They have apparently done these operations from below the diaphragm and illustrate how difficult, if not impossible, it is to completely section the vagus nerves by this route. In none of their cases was the secretion of the stomach or the acidity influenced by partial vagotomy.

Dragstedt and Owens<sup>43</sup> have made a preliminary report on transthoracic interruption of the vagus nerves in ulcer of the stomach and duodenum. It appears that their experimental work and early cases have been further substantiated by a later report on 18 clinical cases.<sup>44</sup> In all these, the patients were relieved of their ulcer symptoms and the ulcers were shown by roentgenographic studies to be healed. There seems to be a definite reduction in gastric secretion and acidity after this procedure.

Moore<sup>45</sup> has accomplished transthoracic vagus interruption in 3 patients at the Massachusetts General Hospital. These were carefully selected as desirable subjects for the procedure and were not

thought suitable for subtotal gastrectomy. The patients are, at this time, greatly improved and are being carefully followed.

#### CANCER OF STOMACH

St. John, Swenson and Harvey<sup>46</sup> examined fluoroscopically 2413 patients beyond the age of forty coming to the outpatient department of the Presbyterian Hospital in New York City for other than gastrointestinal complaints. Three of these were found to have unsuspected malignancy of the stomach — a rate of 1.24 per 1000. In 528, functional and organic lesions other than cancer were discovered. Ninety of these patients had abnormalities within the thorax. The feasibility of this type of examination is discussed. Much depends on the experience of the roentgenologist, and even under ideal circumstances, such studies are unreliable. Many cases of advanced cancer of the stomach have been found within a few weeks after a negative observation. It seems improbable that the high incidence of deaths from cancer of the stomach can be materially lowered by such routine roentgenographic examinations.

Bisgard<sup>47</sup> emphasizes the interrelation of gastric ulceration and cancer of the stomach. The differential diagnosis between ulcer and cancer of the stomach is admittedly difficult and often impossible.<sup>48</sup> Ulcers that appear benign gastroscopically and roentgenologically are often malignant. These lesions appear, at times, to diminish in size, and symptoms improve under treatment; the patient returning, often too late, with obvious cancer of the stomach. The patient with gastric ulcer must be kept under close observation, and delay in surgical interference must be reduced to a minimum. The end results of gastric resection for ulcers that appear benign but prove to be malignant are twice as good as those when the operation is undertaken for obvious clinical cancer. Bisgard further substantiates the fact that gastrectomy is safer for gastric ulcer than for duodenal ulcer and that the results of this type of treatment are more satisfactory than are those of conservative management.

Feldman<sup>49</sup> discusses the life cycle of carcinoma of the stomach. He followed 3 patients over a period of years who had what appeared to be benign gastric ulcer with remissions. Two had relatively low gastric acidity, and the other one had hyperacidity. All these patients eventually developed pyloric obstruction that proved to be due to inoperable cancer of the stomach. He warns against the false security of negative roentgenologic examinations and believes that narrowing of the pylorus may be significant in the absence of a demonstrable tumor. Emphasis is placed on the clinical picture. If the patient is progressively getting worse, frequent observations are necessary until the diagnosis is established.

### INTESTINAL DIVERTICULUMS

Warren and Emery<sup>50</sup> found 103 cases of diverticulum of the duodenum at the Peter Bent Brigham Hospital in Boston over a period of twenty-seven years. This represented an incidence of 2.3 per cent of cases showing roentgenologic evidence of gastrointestinal disease. The average age of the patient was fifty-eight years; 39 were in men and 64 were in women, a reversal of the sex ratio for other duodenal lesions. The size of the diverticulum varied from 0.5 to 6 cm. in diameter; 9 per cent were in the first, 65 per cent in the second and 15 per cent in the third portion of the duodenum, the remainder being multiple. They call attention to a false type in the first portion and a true herniation in the second. The authors believe that many of these lesions are symptomless and that other causes for complaint, such as gallstones, ulcer and pancreatitis, should be ruled out. The treatment for the majority of cases is that used for duodenal ulcer. Only diverticula forming an abscess or failing to empty should be treated surgically.

Pearse<sup>51</sup> presents an excellent description of the surgical management of complicated duodenal diverticula. He illustrates a method of identifying and preserving the opening of the common bile duct and the pancreatic ducts during the procedure. A portion of the neck of the sac is left, as in operations for esophageal diverticula, in order to secure an adequate inversion.

Rudder<sup>52</sup> reports an interesting case of acute diverticulitis of the jejunum. His patient was a fifty-six-year-old Costa Rican farmer who gave a history of postprandial pain of two months' duration. He was hospitalized after three days of intermittent colicky nonradiating epigastric pain and vomiting. The abdomen was flat and rigid, without distention or increased peristalsis. The maximum tenderness was in the midepigastrium. The white-cell count rose from 24,000 on admission to 49,100 within a few hours. The maximum temperature was 101.2° F. The preoperative diagnosis was acute cholecystitis with perforation of the gall bladder. A large acutely inflamed diverticulum was found 45 cm. from the ligament of Treitz. This was excised, and the patient recovered uneventfully.

Young and Young<sup>53</sup> discuss diverticulitis of the colon and, by a compilation of statistics, find that 5.2 per cent of 70,572 patients examined by barium enema or at autopsy showed diverticula. In three series of cases totaling 3915 patients, 34.3 per cent showed inflammation. The majority of patients with diverticulosis can remain symptom free by proper dietary measures and bowel hygiene. They call attention to the apparent transient improvement in symptoms by barium enemas. Approximately 22 per cent of the patients with diverticulitis finally come to surgery for one or more of five reasons, that is, acute perforation with spreading peritonitis, obstruction of the sigmoid, fistula,

localized abscess and inability to rule out cancer. They obtained a history of bleeding in 26 per cent of their cases.

### LYMPHOSARCOMA

McSwain and Beal<sup>54</sup> studied 20 cases of lymphosarcoma of the gastrointestinal tract entering the New York Hospital during a recent nine-year period. These were distributed as follows: esophagus, 1; stomach, 7; small intestine, 3; appendix, 2; and colon and rectum, 7. There were 13 males and 7 females, with ages varying from four and a half to seventy years, — the average being forty-three years. They point out that the correct diagnosis is rarely made preoperatively. Survival is influenced more by the site and extent of the process than by age or the histologic structure of the tumor. Six patients who had well-localized lesions without involved lymph nodes and were treated by excision alone were alive and free of recurrence from two to seven years. Of the 6 patients treated by radiation alone, only 2 were free of recurrence. Two patients were unable to tolerate roentgen therapy and succumbed before treatment was finished. Of the 6 patients treated by excision followed by radiation, 2 were still free of recurrence. Nine of the 20 cases were free of recurrence from one to nine and a half years after the diagnosis was established. Eight patients succumbed with an average duration of two years of life. The authors believe that the best prognosis is in patients who have lesions suitable for complete excision. Roentgen therapy should be used in all cases in which the surgeon and the pathologist are uncertain that the disease has been completely removed.

Winkelstein and Levy<sup>55</sup> studied 15 cases of lymphosarcoma of the intestines and believe that these tumors arise in the lymph nodes or lymph follicles of the submucosa. The mucosal gland structure is obliterated, and the submucosa and muscularis become invaded, which results in a submucosal tumefaction. Stenosis of the small intestine by the tumor is rare, but intussusception is of common occurrence. Lesions affecting the large bowel are prone to produce obstruction. These authors state that the lymph nodes were involved in all their cases. Distant metastases to the liver, spleen and kidneys occurred rarely. They call attention to a characteristic sigmoidoscopic appearance of the tumor, which appears to resemble the surface of the brain. The average age of their patients was forty-four years, and the prognosis was poor even with the best treatment, which they thought to be a combination of surgery and radiation. The typical picture was a history of distention, colicky pain and a slightly tender movable mass.

### MISCELLANEOUS

Kennedy, Dixon and Weber<sup>56</sup> report 11 children from three to fourteen years of age treated for



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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 31061

#### PRESENTATION OF CASE

A fifty-three-year-old toolmaker was admitted to the hospital with substernal pain.

The patient was well until three months prior to admission, when he noted "substernal congestion." This cleared up and he continued to work. About one month later he developed definite substernal pain. Three weeks later he was admitted to another hospital, where all x-ray examinations and studies were said to have been negative. At that time the blood pressure was "elevated." He was told to forget his pain, since no cause for it had been found. The pain continued, however, at irregular times and was not related to meals, exercise or position. It was hard for him to define it more exactly than to say it was bad and that he became fearful that something terrible might happen to him unless it was controlled. He denied cough or dyspnea. He was discharged after a few days, but severe substernal pain persisted. He consulted another physician, who gave him "electrical treatments," which seemed to make him worse. About two weeks before entry he was admitted to another hospital, where roentgenograms and other studies revealed abnormalities that could be responsible for the pain, and he was referred to this hospital for bronchoscopy. He had lost 37 pounds over a period of about three months.

About twelve years before admission he was first found to have slight hypertension. He had been worried about high blood pressure for a long time, since both his parents and two of his grandparents had had it. One brother had died of hypertension and renal failure at the age of forty-four.

Physical examination revealed a healthy-looking man showing evidence of weight loss. There was a

\*On leave of absence

slight Horner's syndrome on the left. The thyroid gland was two to three times its normal size, with a nodule on the right, no bruit was audible over it. There was retromanubrial dullness over an area 8 cm. in width, and slight dullness over the left first and second interspaces. Fremitus and breath sounds were diminished over the left upper lobe. The heart sounds were regular and of fair quality. No murmurs were heard. The abdomen was soft, and no masses or organs were palpable. The femoral pulsations were equal. An examination of the larynx revealed paralysis of the left vocal cord and arytenoid.

The temperature, pulse and respirations were normal. The blood pressure was 180 to 210 systolic, 120 diastolic, and equal in both arms.

Examination of the blood showed a white-cell count of 10,900, with 70 per cent neutrophils, 16 per cent lymphocytes, 7 per cent monocytes and 7 per cent eosinophils. The hemoglobin was 13 gm. The urine had a specific gravity of 1.006, with a + test for albumin; the sediment contained occasional red cells, white cells and hyaline and granular casts. The alkaline phosphatase was 6.9 units per 100 cc. A Hinton test was negative. A phenolsulfonephthalein test showed 20 per cent dye output in fifteen minutes and 10 per cent more in thirty minutes.

By the seventh hospital day the pain had increased and required frequent injections of morphine. He said that it radiated to the midback. A fluoroscopic examination showed a pulsating mass continuous with the aorta, but the left diaphragm appeared paralyzed and showed paradoxical motion. On the tenth hospital day the pain was located about both costal margins. On the twelfth hospital day he was in severe pain, sweating and sitting on the edge of a chair; the pain had extended to the left kidney and to a slight degree into the left leg. Films of the chest revealed an area of increased density, extending from the left hilus into the midchest, that could not be separated from the hilus or the descending aorta (Fig. 1). The edge was sharply demarcated, and there seemed to be some atelectasis of the lung around it. The density pulsated with the aorta, but the descending aorta could be traced through it. The left leaf of the diaphragm was elevated and again showed paradoxical motion. The lung fields were otherwise clear.

On the morning of the thirteenth hospital day the patient suddenly coughed up 4 to 8 cc. of blood-



diagnosis. I should put the neoplasm in the bronchus of the upper lobe.

Three or four months before admission, x-ray studies were negative, which is perfectly all right for a bronchial neoplasm that is concealed in the mediastinum and therefore not seen during fluoroscopy or on the first x-ray plate. The patient then began to have signs of obstruction of the left upper lobe, with atelectasis, and associated with that he began to have signs of a sulcus tumor. He had paralysis of the recurrent laryngeal nerve on the left and paralysis of the diaphragm on the left, all of which suggest invasion of the left mediastinum. This, of course, might have been a lymphangitic type of carcinoma of the lung, in which case I could not differentiate it without seeing the x-ray films. Then the patient coughed up bloody sputum and began to get central-nervous-system signs, which could have been caused by an embolus. An infected cerebral embolus fits in well with the Jacksonian epilepsy and the high temperature. There is no suggestion of anything wrong with the heart, and nothing suggestive of a mycotic aneurysm or subacute bacterial endocarditis. The Jacksonian epilepsy and nerve palsies, however, could also have been due to a silent cerebral metastasis, with hemorrhage into it. One other reason for the diagnosis of bronchiogenic neoplasm lies in the blood phosphatase level, which is double the normal. When a carcinoma of the bronchus breaks into a pulmonary vein, the tumor is distributed all over the body. It not infrequently gets into the bones, where it usually forms an osteoclastic lesion, but there is no reason why there cannot be an osteoblastic reaction, which would give an elevated phosphatase level in the blood.

This man probably had a bronchiogenic neoplasm in the left upper bronchus, with atelectasis and possibly pneumonia or abscess behind it to account for the fever. I think that he also had metastases, probably widespread, involving bone—it is usually in the vertebrae, in spite of the negative x-ray evidence—and the right cerebral region, with slight hemorrhage into the latter. I believe that he had contracted kidneys, which produced a urine of low, fixed specific gravity, but that this was of secondary importance.

May I now see the x-ray films?

DR. CHESTER M. JONES: Does the fact that pulsation of the dorsalis pedis artery was demonstrated argue against dissecting aneurysm?

DR. AUB: Yes. I looked throughout the history for evidence of some vessel that was obstructed but could find none.

DR. WYMAN RICHARDSON: My bet is aneurysm.

DR. LAURENCE L. ROBBINS: I appreciate Dr. Aub's confidence in diagnosis by x-ray examination, because differentiation of cancer of the left-upper-lobe bronchus and aneurysm is one of the most difficult to make. I have put up the films that were done elsewhere to show the development of the

process. This is a chest examination, which was interpreted as negative. These films were taken approximately one month later, and there has been a definite change, the left diaphragm being elevated. The films that were taken at this hospital demonstrate certain things that may be of help. This is the mass in the medial portion of the left-upper-lung field that was seen and interpreted in various ways. The fluoroscopist said that he was unable to separate it from the hilus or from the aorta. These overexposed films give a rather clear picture of the entire descending portion of the aorta. There is one other finding that may be of some value; that is, you can see a small portion of the septum between the upper and the lower lobes on the left side, and it is definitely anterior to the normal position.

DR. AUB: What does that tell us?

DR. ROBBINS: That the left upper lobe is somewhat decreased in size.

DR. AUB: You are not so helpful as I thought you were going to be.

DR. JONES: Does one get laryngeal paralysis from aneurysm? Would that mean infiltration around the nerve.

DR. AUB: The nerve involvement strongly suggests neoplasm. In fact, these x-ray studies make me disagree with Dr. Richardson.

#### CLINICAL DIAGNOSES

Dissecting aortic aneurysm, with compression of the left-upper-lobe bronchus.  
Cerebral hemorrhage, right.  
Hypertensive heart disease.

#### DR. AUB'S DIAGNOSES

Bronchiogenic carcinoma, left upper lobe, with metastases to mediastinum, bones and right cerebrum.  
Atelectasis of left upper lobe of lung (? abscess).  
Nephrosclerosis.

#### ANATOMICAL DIAGNOSES

Oat-cell carcinoma of the lung, left upper lobe, with extension to the mediastinal structures and pericardium and with metastases to the bronchial, mediastinal and retroperitoneal lymph nodes, adrenal and thyroid glands and vertebral spine.  
Cardiac hypertrophy, hypertensive type.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this patient proved that Dr. Aub was correct. This man did have a tumor involving the left upper lobe, most of it extending into the mediastinum. The mediastinal extension and involved mediastinal lymph nodes had invaded the pericardium and surrounded portions of the arch of the aorta, encroaching on the

streaked frothy sputum. A few hours later, while lying flat for dorsal-spine films, he suddenly twisted his head to the left, had convulsive movements and became cyanotic and had stertorous breathing. These films showed marked proliferative changes

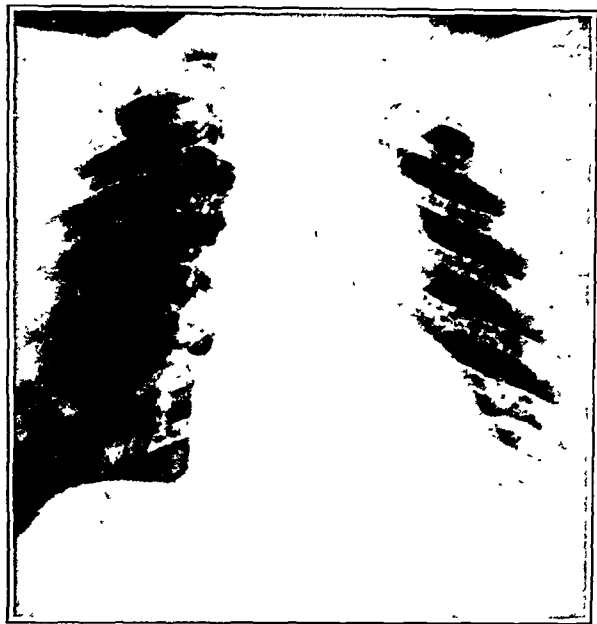


FIGURE 1.

but no definite areas of erosion or destruction. The medial border of the left lung, normally lying close to the spine, was seen to be at least a centimeter away from it. Following this there was paresis of the left side.

During the next few hours he had four or five Jacksonian seizures, beginning on the left side of the face and extending to the left arm, left leg, right arm and right leg. A few were mild and terminated with the left arm. He vomited after one seizure. Between attacks there was weakness of the left arm and leg and he was irrational, restless and noisy. There was some nuchal rigidity. The pupils were equal. The fundi could not be examined. After 400 cc. of blood were removed by venesection, the blood pressure was 130 systolic, 85 diastolic. The femoral and dorsalis-pedis pulsations were equal. A lumbar puncture revealed clear colorless fluid under a high initial pressure. Following the removal of 10 cc. the final pressure was equivalent to 400 mm. of water. The temperature rapidly rose to 105°F., and the blood pressure returned to the original level. The patient continued to cry out because of pain in the back, and the left-sided paresis persisted. He became incontinent and finally died on the fifteenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB: I shall not ask to see the x-ray films because I think that they would probably disclose the diagnosis.

The Horner's syndrome is extremely important if true; but it is never spoken of again, and I should like to be sure that it was really there and not a mere asymmetry.

DR. BENJAMIN CASTLEMAN: Dr. Chapman, will you tell us about that?

DR. EARLE M. CHAPMAN: There was a slight but definite Horner's syndrome.

DR. AUB: With a loss of 35 pounds of weight one has to consider an overactive thyroid gland; there is no suggestion of this except its large size. I think that retromanubrial dullness involves one of the most difficult areas in the chest for percussion, but I shall accept the statement of increased dullness to 8 cm. All the chest findings suggest that this man had collapse of the left upper lobe.

We then learn that he had paralysis of three nerves that can be involved in the mediastinum, namely, the cervical sympathetic nerves, producing a Horner's syndrome, the recurrent laryngeal nerve and the phrenic nerve.

The value for alkaline phosphatase was twice the normal. That is undoubtedly important. One does not usually observe such a finding unless there is some reasonable explanation for it.

The attacks of cyanosis and stertorous breathing were obviously thought to be due to hypertension or to cardiac failure. I do not believe that the rest of the story sounds as if he had a cardiac lesion or cardiac failure. The hypertension was such as might well precede the cerebral attacks that he had. I suppose that is the reason they bled him, but it did little good, as might have been expected.

This is an extremely difficult case. One can argue about many things that this might have been, either in the brain, in the chest or elsewhere. I think on the whole, however, that it is best to discuss only two conditions, — aneurysm of the aorta and carcinoma of the lung, — realizing that by so doing I may completely miss the diagnosis.

Did he have an aneurysm? He had an examination three months before entry and nothing abnormal was found. If he had had an aneurysm it ought to have been observed at that time. The Hinton test was negative. Under these conditions it seems unlikely to me that he had an aneurysm of the syphilitic type, but he might have had a dissecting aneurysm. The pain gradually migrated from the chest to the kidney region and down toward the pelvis, but there is no good evidence of the closing off of any peripheral blood vessels. The whole story seems to me to be much too slow and protracted for that of a dissecting aneurysm, although I admit that dissecting aneurysm appears to be a perfectly tenable diagnosis: the patient had hypertension, he was the proper age, the story is suggestive of the way the usual pain of dissecting aneurysm is distributed, and the clinical course is also suggestive.

Carcinoma starting in one of the main bronchi of the left lung, however, appears to be a much likelier

diagnosis. I should put the neoplasm in the bronchus of the upper lobe.

Three or four months before admission, x-ray studies were negative, which is perfectly all right for a bronchial neoplasm that is concealed in the mediastinum and therefore not seen during fluoroscopy or on the first x-ray plate. The patient then began to have signs of obstruction of the left upper lobe, with atelectasis, and associated with that he began to have signs of a sulcus tumor. He had paralysis of the recurrent laryngeal nerve on the left and paralysis of the diaphragm on the left, all of which suggest invasion of the left mediastinum. This, of course, might have been a lymphangitic type of carcinoma of the lung, in which case I could not differentiate it without seeing the x-ray films. Then the patient coughed up bloody sputum and began to get central-nervous-system signs, which could have been caused by an embolus. An infected cerebral embolus fits in well with the Jacksonian epilepsy and the high temperature. There is no suggestion of anything wrong with the heart, and nothing suggestive of a mycotic aneurysm or subacute bacterial endocarditis. The Jacksonian epilepsy and nerve palsies, however, could also have been due to a silent cerebral metastasis, with hemorrhage into it. One other reason for the diagnosis of bronchiogenic neoplasm lies in the blood phosphatase level, which is double the normal. When a carcinoma of the bronchus breaks into a pulmonary vein, the tumor is distributed all over the body. It not infrequently gets into the bones, where it usually forms an osteoclastic lesion, but there is no reason why there cannot be an osteoblastic reaction, which would give an elevated phosphatase level in the blood.

This man probably had a bronchiogenic neoplasm in the left upper bronchus, with atelectasis and possibly pneumonia or abscess behind it to account for the fever. I think that he also had metastases, probably widespread, involving bone—it is usually in the vertebrae, in spite of the negative x-ray evidence—and the right cerebral region, with slight hemorrhage into the latter. I believe that he had contracted kidneys, which produced a urine of low, fixed specific gravity, but that this was of secondary importance.

May I now see the x-ray films?

DR. CHESTER M. JONES: Does the fact that pulsation of the dorsalis pedis artery was demonstrated argue against dissecting aneurysm?

DR. AUB: Yes. I looked throughout the history for evidence of some vessel that was obstructed but could find none.

DR. WYMAN RICHARDSON: My bet is aneurysm.

DR. LAURENCE L. ROBBINS: I appreciate Dr. Aub's confidence in diagnosis by x-ray examination, because differentiation of cancer of the left-upper-lobe bronchus and aneurysm is one of the most difficult to make. I have put up the films that were done elsewhere to show the development of the

process. This is a chest examination, which was interpreted as negative. These films were taken approximately one month later, and there has been a definite change, the left diaphragm being elevated. The films that were taken at this hospital demonstrate certain things that may be of help. This is the mass in the medial portion of the left-upper-lung field that was seen and interpreted in various ways. The fluoroscopist said that he was unable to separate it from the hilus or from the aorta. These overexposed films give a rather clear picture of the entire descending portion of the aorta. There is one other finding that may be of some value; that is, you can see a small portion of the septum between the upper and the lower lobes on the left side, and it is definitely anterior to the normal position.

DR. AUB: What does that tell us?

DR. ROBBINS: That the left upper lobe is somewhat decreased in size.

DR. AUB: You are not so helpful as I thought you were going to be.

DR. JONES: Does one get laryngeal paralysis from aneurysm? Would that mean infiltration around the nerve.

DR. AUB: The nerve involvement strongly suggests neoplasm. In fact, these x-ray studies make me disagree with Dr. Richardson.

#### CLINICAL DIAGNOSES

Dissecting aortic aneurysm, with compression of the left-upper-lobe bronchus.

Cerebral hemorrhage, right.

Hypertensive heart disease.

#### DR. AUB'S DIAGNOSES

Bronchiogenic carcinoma, left upper lobe, with metastases to mediastinum, bones and right cerebrum.

Atelectasis of left upper lobe of lung (? abscess). Nephrosclerosis.

#### ANATOMICAL DIAGNOSES

Oat-cell carcinoma of the lung, left upper lobe, with extension to the mediastinal structures and pericardium and with metastases to the bronchial, mediastinal and retroperitoneal lymph nodes, adrenal and thyroid glands and vertebral spine.

Cardiac hypertrophy, hypertensive type.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this patient proved that Dr. Aub was correct. This man did have a tumor involving the left upper lobe, most of it extending into the mediastinum. The mediastinal extension and involved mediastinal lymph nodes had invaded the pericardium and surrounded portions of the arch of the aorta, encroaching on the

phrenic nerve. The part of the upper lobe not replaced by the tumor was collapsed.

The tumor involved the bronchus to the left upper lobe and proved to be an oat-cell type of carcinoma, which is prone to surround and invade the bronchial walls with only slight intraluminal tumor, which was true here. As Dr. Aub also predicted, the vertebral spine was practically replaced by tumor and showed a great deal of osteoblastic proliferation and fibrosis, which accounted for the elevated phosphatase.

There were metastases to the adrenal and thyroid glands. The brain showed no evidence of metastasis grossly. There was a hemorrhagic lesion in the left parietal lobe, which I do not suppose accounted for the symptoms. The microscopic sections have not been finished, but grossly it did not look like a metastasis.

DR. AUB: I suppose that the hemorrhage was on a hypertensive basis.

DR. CASTLEMAN: He did have a large heart of the hypertensive type.

DR. CHAPMAN: I want to pay tribute to Dr. Aub for his astute interpretation of the findings, which led to the correct diagnosis. I learned three things from this case that were clinically important. The first is that the nerve paralyses were not caused by a dissecting aneurysm but by the cancer. The second point, which Dr. Aub brought out in interpreting the history, is that the pain was too dragged out and too long to be the pain of a dissecting aneurysm. Dr. Castleman called that to my attention when the case was autopsied. The third point is that the clinical impression should outweigh conflicting x-ray evidence that later comes into the picture.

I started out with a diagnosis of cancer of the upper lobe with obstruction to the bronchus but ended up with a diagnosis of aneurysm. I changed my opinion because when this man was fluoroscoped they said that it was an aneurysm. The appointment for a bronchoscopy was therefore canceled and a definite diagnosis of aneurysm was made. Then the patient was fluoroscoped by Dr. Schulz, who thought that the lesion was cancer; his reasons were that, although he could not differentiate the mediastinal mass, the nerve paralysis, the paralysis of the diaphragm and the separation of the lobe were strongly in favor of cancer of the lung root.

DR. CASTLEMAN: I do not believe that we have ever seen paralysis of a nerve with a dissecting aneurysm. In dissecting aortic aneurysm the aneurysm itself is not particularly large. It is not as a rule a bulbous affair, such as is present in the ordinary syphilitic or arteriosclerotic aneurysm. Occasionally one finds a small hematoma but certainly nothing so large as to affect or infiltrate a nerve. I think that is a good point.

DR. J. H. MEANS: Does a Horner's syndrome occur in aneurysm?

DR. CASTLEMAN: It may be present with a syphilitic aneurysm but not with a dissecting aneurysm.

## CASE 31062

### PRESENTATION OF CASE

A nineteen-month-old infant was brought to the hospital because of respiratory distress of four and a half hours' duration.

The patient had had a mild cold with no constitutional symptoms for two days. Four and a half hours before admission she developed respiratory distress. This steadily progressed to such an extent that she was brought to the hospital.

Physical examination showed a well-developed, well-nourished, cyanotic infant in acute respiratory distress, gasping for breath. Suprasternal and abdominal retractions were seen with every respiration. The voice was not hoarse. The lungs were clear except for a few coarse and some musical rales audible throughout. The throat was brilliant red. The epiglottis was red and edematous. Examination was otherwise negative.

The temperature was 100°F. (the child had had aspirin); the pulse and respirations were not recorded.

The white-cell count was 25,000. X-ray film of the chest showed a mottled increase in the density of both lower lung fields. The stomach was slightly dilated.

About an hour after admission a 4-mm. bronch scope was passed down to the trachea with extreme difficulty; the entire mucosa was red. A tracheotomy was attempted, but the patient died about one minute before the tube was inserted.

### DIFFERENTIAL DIAGNOSIS

DR. ERNA ANDERSON: We have a story of an infant with acute infection running such a fulminating course that four and a half hours after the onset of symptoms there was extreme respiratory distress with retractions, cyanosis and gasping respirations. Two conditions are brought to mind that might cause this sequence of events, namely, interstitial pneumonia and laryngotracheobronchitis.

Interstitial pneumonia is an infection frequently seen in infants one year of age or younger, but not infrequently seen in this age group. It is characterized by sudden onset of rapidly increasing distress, with dilatation of the alae nasi and retractions, both suprasternal and subdiaphragmatic. The temperature is variable; the fever may be low, or the temperature may be elevated to 102 or 103°F. The respirations are rapid and shallow. The chest is held in an inspiratory position, but the excursions are limited. On physical examination, rales are heard everywhere. The signs are somewhat generalized. This is a condition in which the interstitial tissue of the lungs is involved, being characterized by patchy areas of atelectasis and emphysema. The signs are not constant. The white-cell count may be normal or slightly elevated. A count of 25,000 is rather high.

The other condition, laryngotracheobronchitis, covers a variety of infections. The most frequent is ordinary mother's croup; this occurs usually at night after the child who has gone to bed feeling apparently well awakens with a hoarse barking cough and may show some evidence of respiratory distress. This disease is generally mild; the symptoms usually subside the following day but may recur again at night. There may or may not be an elevation of temperature.

A severer form of this type of infection is the laryngotracheobronchitis characterized by subglottic edema. In this, again, the onset may be sudden. In general the course is less fulminating than that mentioned in the present case, and the child may be in the hospital for a period of hours before the wisdom of tracheotomy is determined. The temperature may or may not be elevated but is usually about 102 or 103°F. The white-cell count may be normal or slightly elevated. Again, I believe that a count of 25,000 is a little high for that type of laryngotracheobronchitis. It occurs in the age group between one and two years, there is usually no dilatation of the alae nasi, and the child is almost always hoarse.

A third type of infection is characterized by edema and swelling of the epiglottis. This is really an epiglottitis rather than a laryngotracheobronchitis. It is usually seen in children over two years of age, but Sinclair,\* reporting his experience at the New Haven Hospital, mentions that it may occur in children as young as four and a half months. The onset is characteristic, with sudden symptoms that progress to a point where tracheotomy is necessary for relief of respiratory distress from four to twelve hours after the onset. There is a peculiar gasping type of respiration, with implication of the accessory muscles of expiration, as well as sub-sternal and abdominal retractions. Dilatation of the alae nasi is usually not seen. The chief complaint is sore throat and dysphagia. Probably this child was too young to make such complaints. Since the infection usually occurs in the epiglottis, above the larynx, hoarseness may not be present since the vocal cords may not be involved. There is usually fever of an extreme degree, 103 to 105°F., and marked leukocytosis, which ranges from 15,000 to 40,000. The children are extremely prostrated and show evidence of overwhelming infection, and in severe cases there may be an associated pneumonia.

In the information we have it has not been mentioned whether or not there was dilatation of the alae nasi. I wonder if we can find out about that.

DR. GERTRUD REYERSBACH: There was dilatation of alae nasi.

DR. ANDERSON: That means that there was extreme respiratory distress, probably pneumonic

rather than tracheal. May we look at the x-ray films?

DR. BENJAMIN CASTLEMAN: There is no radiologist here.

DR. ALLAN M. BUTLER: The report states: "There is definite increase in density in both lower lung fields. The density is mottled in appearance and possibly represents an aspirated pneumonia. The stomach appears to be slightly dilated."

DR. ANDERSON: There is a hazy increase in the markings, as well as the patchy areas of increased density that are mentioned. I was particularly interested to see if there was any evidence of emphysema. It is not mentioned in the report, nor does it appear so to me in the films. The lung fields are not overly clear, and the intercostal interspaces do not seem particularly widened. The position of the diaphragm is relatively normal rather than depressed as one would expect with emphysema. So I think that we can say there was probably no emphysema. The appearance of the x-ray films is not characteristic of interstitial pneumonia. Although some points favor such a diagnosis, the facts that the throat was brilliantly red and the epiglottis red and edematous make me think that this probably falls into the group of cases in which the infection is in the tracheal tree.

It is, of course, of great practical importance to differentiate interstitial pneumonia and laryngotracheobronchitis. In the former condition the obstruction is in the finer radicles and tracheotomy does not help the symptoms, whereas with subglottic or epiglottic obstruction, improvement of the airway below the larynx relieves the respiratory distress. Apparently the service thought that a tracheotomy would be helpful.

Acute epiglottitis is an infectious disease caused by one agent, *Haemophilus influenzae*, and in the reported cases there has always been an associated bacteremia. In spite of the fact that this child was somewhat young, she probably had that disease. It seems likely that the immediate cause of death was laryngospasm, with failure of respiration due to the obstruction. The explanation for this is unsatisfactory. It is assumed to be on a reflex basis. We know clinically that children with laryngeal obstruction are particularly susceptible to laryngospasm, and we hesitate to perform certain procedures without arrangements for immediate tracheotomy at hand. This applies to a digital puncture for obtaining a blood count, to venous puncture for obtaining blood cultures and to swabbing of the nose and throat for culture; it even extends to precautions that should be taken in examination of the pharynx, in which case it is better to use a finger rather than a tongue stick.

I believe that this child had acute epiglottitis, probably due to *H. influenzae*, with associated bacteremia and bronchopneumonia.

DR. BUTLER: I should like to say that this is an

\*Sinclair, S. E. *Haemophilus influenzae* type B in acute laryngitis with bacteremia. *J. A. M. A.* 117:170-173, 1941



phrenic nerve. The part of the upper lobe not replaced by the tumor was collapsed.

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## NONESSENTIAL NURSING

IN most departments of social activity it is possible to distinguish between what is essential to the war effort and what is not — especially now that our needs and deficiencies have become so plain. To separate essential from nonessential nursing, however, is a difficult and highly professional matter.

Registered nurses are employed by many physicians for more or less routine office work. Furthermore, there always have been people who indulged themselves unnecessarily in hospital and nursing service; this was an easy thing to do for anyone who could pay his bills, and money is freer now than it ever was before. Luxuries in other fields have been

abolished or rationed, but every practicing physician knows that the abeyance of psychoneurotic complaints that characterized the English blitz of 1940 has no counterpart here.

Some trades and professions have been hit harder than others by the changes of war, but one after another they have managed to meet their national obligations when the squeeze came. The nursing profession is now caught in one of these pinches, and we are beginning to see such headlines as "46 NURSES CARE FOR 1689 WOUNDED." Although most physicians realize that statements of this sort are misleading, since they do not take into account the service given by medical corpsmen, the War Manpower Commission states that 10,000 nurses are urgently needed, and it has been determined on the basis of registered-nurse populations that Massachusetts should supply 969 of these. The Massachusetts Committee for Nurses of the Procurement and Assignment Service has worked hard and long, classifying and reclassifying the women who should be able to meet this crisis. Many who are believed by the committee to be available, however, continue to do what is obviously nonessential nursing. How many registered nurses in doctors' offices are doing work that could not be equally well handled by a medical secretary? How many patients are hospitalized unnecessarily? How many nurses could be freed if their use in private cases were limited to those in which they are really essential?

The first question can be answered only by physicians, and the remedy, if needed, can only be supplied by them. The other questions are being asked by many, and will become more and more widespread as the months of 1945 pass. The Boston City Hospital has begun its answer by insisting that all requests for the assignment of special nurses pass through the hands of the senior visiting physician or surgeon. Other hospitals might follow, or might use other methods. Whole wards for civilian patients might well be closed. Elective surgery might be banned for the duration. For these or for other methods of meeting this emergency the action that will effectively answer the question *must* come from physicians. Every nurse works under a doctor's supervision — and must work with

excellent example of the type of case that demands immediate diagnosis and immediate tracheotomy. The diagnosis apparently was made when this child entered the hospital, since the Emergency Ward note by the pediatric resident states, "The diagnosis is epiglottitis, probably the influenzal type." A nose-and-throat consultant was called, and the child was immediately transferred to the Massachusetts Eye and Ear Infirmary for tracheotomy.

DR. JACOB LERMAN: I should like to ask whether intubation is a practice here rather than tracheotomy.

DR. ANDERSON: I do not believe that intubation is done. At any rate in this case intubation was contraindicated because the obstruction was high and the epiglottitis would still have caused obstruction after intubation.

DR. BUTLER: The real therapy is immediate tracheotomy. The diagnosis can usually be made instantly if the physician thinks of the possibility. The history and the clinical picture are typical. The findings, particularly the large, cherry-red, swollen epiglottitis, are practically diagnostic.

DR. ANDERSON: I should like to say that in the reported cases there have been three or four in which recovery has been accomplished without tracheotomy, but all these patients were over five years of age.

DR. CASTLEMAN: Do they give serum or sulfonamide therapy?

DR. ANDERSON: Serum has been given only in the cases in which the infection was overwhelming. Patients in whom tracheotomy is not warranted usually get along well on sulfadiazine.

#### CLINICAL DIAGNOSES

Acute epiglottitis (*H. influenzae*).  
Septicemia (*H. influenzae*).

#### DR. ANDERSON'S DIAGNOSES

Acute epiglottitis (*H. influenzae*).  
Septicemia (*H. influenzae*).  
Bronchopneumonia.

#### ANATOMICAL DIAGNOSES

Acute epiglottitis (*H. influenzae*, Type B).  
Septicemia (*H. influenzae*, Type B).  
Interstitial pneumonia.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy findings on this child were exactly as Dr. Anderson predicted. There was a marked inflammatory reaction in the epiglottis, which was edematous and fiery red. Microscopic examination showed an extreme degree of inflammation, with polymorphonuclears, practically an abscess, involving the epiglottis. Strangely enough there was relatively little infiltration in the main bronchi, but microscopic sections of the lungs showed a definite infiltration around the smaller bronchioles throughout the lung with lymphocytes, monocytes and a few polymorphonuclears. Therefore, I shall have to make an additional diagnosis of interstitial pneumonia, although it had not progressed sufficiently to give areas of atelectasis and emphysema, such as one usually sees.

A culture of the epiglottis was taken during life but had not been reported by the time the patient died; it yielded *Haemophilus influenzae*, Type B. The spleen was enlarged and showed evidence of acute splenitis.

DR. REYERSBACH: Culture of the heart's blood at autopsy also showed *H. influenzae*?

DR. CASTLEMAN: Yes.

DR. ANDERSON: Did you culture the lungs?

DR. CASTLEMAN: No.

DR. ANDERSON: Sinclair reports that *H. influenzae* was cultured from the lung in some cases that had failed to show pneumonia microscopically, but I suppose that this might be explained on the basis of a positive blood culture.

DR. CASTLEMAN: The pneumonia that one observes in this condition is not the type in which the alveoli are filled with exudate; the infiltration is around the bronchi in the interstitial tissues.

DR. CHESTER M. JONES: The lungs might yield a positive culture in the absence of pneumonic consolidation if the disease process were very early, death occurring before the pneumonia had developed.

DR. ANDERSON: That is what Sinclair attributed the positive cultures to.

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## WHAT ABOUT HEALTH INSURANCE?\*

ROGER I. LEE, M.D.

BOSTON

WORDS may be used to conceal a real meaning, sometimes intentionally and sometimes unintentionally. This is particularly true of those combinations of words that become slogans. This tendency is as old as words themselves, especially if there is a political relation. With the passage of time, a phrase often comes to connote something quite different from the actual meaning of the words. For example, the catch phrase "health insurance" really means quite the reverse; it is insurance to be used when one is sick. Now, the popular connotation of the term is the provision of medical care of some sort, whereas most other plans of insurance provide a cash indemnity or benefit. Certainly this is the connotation of life, fire, theft and other types of insurance. This is what the United States Government proposed to do when it offered insurance against enemy damage to property. If a social organization takes out rain insurance for its annual outdoor strawberry festival, in case of rain the organization gets a cash indemnity. Yet the state of Rhode Island's cash sickness-compensation plan is often designated as a health or sickness insurance plan, with the erroneous assumption that it provides either medical care or the money for that care, whereas the plan provides cash when the worker is ill.

One important reason for some of this confusion is doubtless that sickness is not easily defined. The so-called "private" insurance companies have been wrestling with this problem for many years. From the point of view of these companies, death is a definite affair, fire is somewhat less so, theft leads on to troubled ground, and sickness is a real difficulty. In so-called "life insurance," really death insurance, there is rarely doubt about the death of the insured person. To be sure, in rare instances there has been substitution and even the murder of an insured person for the insurance money. Then, too, there is the occasional person who, when he is told by a physician that he cannot survive, promptly takes out as large an insurance on his life as he can carry. But these cases are unusual, and the insurance com-

panies are constantly putting increased safeguards against such practices.

In the less well-defined forms of insurance, one finds that the insurance companies have had to develop elaborate safeguards to counteract the cupidity and venality of some persons. It takes years to develop these safeguards. For example, the situation of automobile liability insurance is still confused and unsatisfactory in many ways. If and when automobile insurance becomes reasonably satisfactory with increased experience, there will be airplane insurance to be grappled with.

It has taken years to bring a semblance of order out of the workmen's compensation laws and regulations. There are complicated problems, some of which involve the relations of insurance-company doctors with private physicians, as well as the rights of the workingman to his freedom of choice of a physician. Although progress has been made, I believe that no one would claim that the situation is perfect or even satisfactory.

We are now in the midst of a war of extraordinary magnitude. So far as I know, no one questions the obligation of the Government to care generously for the soldiers who have suffered in the defense of their country. Most of us, I think, are prepared to give our soldiers the benefit of any doubt, so that any sifting device does not eliminate the worthy-soldiers, even if some perhaps unworthy persons slide through. But even Congress seems confused concerning how far this insurance goes and what the distinction is between insurance against risks of war in the armed forces and so-called "security," however this may be defined, for soldiers and war workers at home. Certainly a grateful government must treat the disabled veterans liberally. If the experiences after other wars are any indicators, however, there will be many problems and many difficulties, and not all of them will be solved to the satisfaction of those concerned.

Some of these difficulties and problems will stem from misunderstandings and from differences in interpretation of the wording of some of the laws and of some of the regulations and directives. Others will arise directly from a lack of agreement about

\*An address delivered at a meeting of the Suffolk District Medical Society, Boston, November 18, 1944.

his tacit approval, not only of her knowledge and skill but also of her very employment.

When the questions reach the ears of the public, the answers will have to be those that the public dictates. The doctors should begin to frame answers that are not equivocal. Until the war is over, physicians should *not* employ nurses in their offices if the work can be done by others, civilians should *not* go to hospitals simply because they can have their bills paid, and private nursing care should *not* be permitted unless the patients are critically ill. These are the answers that the public should and will demand.

### CANNED HEALTH BROADCASTS

TRUE to the concept that health is a public commodity and that its promotion and preservation should be under the stewardship of the medical profession, the Bureau of Health Education of the American Medical Association offers a new public-address service to state and local medical societies. It has long been a function of the bureau to furnish scripts to be delivered as speeches by local physicians or to be used as rewrite material, but the supply of available local speechmakers is running short. The doctors, interested as they may be in education of the laity, have been forced to streamline their activities; the care of sickness has become a more pressing problem than instruction in the preservation of health.

The new service of the bureau consists, up to the present time, of four series of electrically transcribed radio broadcasts for use in broadcasting to the public and one series for use in connection with health teaching in elementary schools. Complete sets of the records for public broadcasting are available to medical societies as a free loan service, the cost being only that of shipping; the "Health Heroes" set for school use is offered for sale only, at a cost of \$25 per set of twelve programs. In order that this set can be used, the school must have a broadcasting system or a portable record player, or arrangements must be made with a local radio station.

It is reassuring, in these days of social and political unrest, when no one knows what the future may hold for any of us, to realize that our youthful parent

society stands squarely behind a policy of public information. It is further to be expected that when a sound system of medical socialization is presented organized medicine will back that, also, with a right good will.

### NOTICES

#### TUFTS MEDICAL ALUMNI LECTURE

The annual alumni lecture will be given at Tufts College Medical School on Wednesday, February 28, at 4 p.m. Dr. James W. Manary will speak on the subject "The Roads—New and Old."

Physicians and students are cordially invited to attend.

#### GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Wednesday, February 21, at 8:15 p.m. There will be a symposium on recent advances in endocrinology.

##### PROGRAM

Thiouracil in Thyrotoxicosis. Dr. E. B. Astwood.  
Gynecologic Endocrinology. Dr. George Van S. Smith.  
Pediatric Endocrinology. Dr. Richard Wagner.

#### NEW ENGLAND ROENTGEN RAY SOCIETY

The next meeting of the New England Roentgen Ray Society will be held at the Harvard Club of Boston on Friday, February 16. There will be an x-ray conference at 4:30 p.m. At 8:00 p.m., Dr. Henry L. Jaffe will speak on the subject "Osteoid Osteoma."

#### HEALTH-OFFICER FELLOWSHIPS

The Commonwealth Fund, of New York City, has recently announced the provision of six fellowships for the training of health officers. All applicants must possess a medical degree, have had at least one year's internship and have shown ability together with interest in and aptitude for public health, men who have had at least a few months' experience in actual public-health work being preferred. Applicants without any experience in public health must have exceptional ability, and if awarded a fellowship, will be provided a full calendar year so that they may have opportunity for some field training either before or after the course of study. Applicants who have not attended a school of public health will be preferred, and the fellowships will be awarded for one school year, except as indicated above. Applicants who have attended a school of public health for one year will be considered for a second year, for the doctorate provided there are available fellowships. The stipends will be \$175 to \$200 a month for single men and \$200 to \$250 a month for married men, depending on circumstances, plus tuition and travel from home to school and return.

Application blanks and further information may be obtained from the Division of Public Health, Commonwealth Fund, 41 East 57th Street, New York 22, New York.

#### SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 15

##### FRIDAY, FEBRUARY 16

\*9 00-10 00 a.m. Dwarfism. Dr. Nathan Talbot. Joseph H. Pratt Diagnostic Hospital.

10 50 a.m. Use of Antibiotics in Dermatology. Dr. G. E. Mori (Postgraduate clinic in dermatology and syphilology). Amp theater, Mallory Building, Boston City Hospital.

##### SATURDAY, FEBRUARY 17

\*10 00 a.m.-12 00 m. Medical staff rounds. Peter Bent Brigham Hospital.

(Notices continued on page xix)

the meaning of words and the inability to define precisely certain terms, such as "wound," "injury" and "sickness." The addition of the phrase "service-incurred disabilities" adds to the confusion. I recount these facts without comment, certainly no adverse comment, because it seems to me to help to clarify thinking on the whole insurance situation that is developing before us.

The inability to define illness precisely has always been a bugaboo of the medical profession. Even as medical science has progressed in the precision of diagnosis, there is always a shifting no-diagnosis land. In some cases it seems right in front of one; again, it seems just on the horizon. Doubtless it furnishes sustenance to quackery and charlatanism. The story is told of Dr. Henry J. Bigelow at the Massachusetts General Hospital, according to which a desperately ill patient, who had been treated by an irregular practitioner for "rheumatism of the liver," was admitted to the hospital. At the autopsy, on the insistence of Dr. Bigelow, the physician appeared. The liver was quite normal. Dr. Bigelow turned to the quack and made some scornful remarks. The quack replied: "Yes, Dr. Bigelow, the liver is normal. I cured that liver. I wish you had done as well with the malady that killed the patient." The medical profession points to the fantastic accounts of cures of various cults as evidence not usually of mistaken diagnoses on the part of doctors, but rather of the mistaken and often honest beliefs on the part of patients that they were really sick. Such convictions are sometimes dislodged by an emotional impact that is part of the stock in trade of the cultists.

The medical profession is therefore not surprised at the difficulties arising from the inability to define sickness in the area of insurance. Experience has taught that, whereas statistics may show a definite rate of sickness, under conditions of insurance this rate is increased, perhaps doubled or trebled. Furthermore, the explanation does not entirely lie in the fact that medical service without the fee-for-visit arrangement will reveal otherwise neglected sickness. Nor does the explanation depend entirely on the desire to get a return on money expended for insurance protection. It is necessary to study and digest these actuarial figures. The same difficulty is encountered in every army that supplies medical service for all and has no fee-for-service arrangement, particularly in the case of troops who are undergoing training that is vigorous, with the quality of leadership leaving something to be desired. We call it harsh orders, ill-advised punishments and scanty morale. Low morale occurs everywhere at times. Perhaps the psychiatrist and social worker have ages, the doctors have recognized all this and more. sympathy and firmness are helpful. Through the therapeutic measures in or out of the Army, but and "tough" medical considerations are not effective in obstetrics, in acute illnesses like pneumonia, in the hospitalization of fractures and in surgical operations for acute conditions. It is popular because it helps pay for the acute catastrophic emergencies. It does not pay doctors' bills — sometimes, I fear, to the surprise and disappointment of the subscribers. It does not pay for sickness outside the

tramps with many complaints.

But the insurance principle has in general worked well in a good many areas. Consequently, there was inevitably further trial of this principle in sickness. The large private insurance companies have experimented extensively with it. Despite substantial progress, I believe it to be true that the inherent difficulties and problems have not been solved and that accurate and reliable actuarial figures are still lacking. One substantial obstacle has been the lack of an explicit and usable definition of sickness. Certain applications of the insurance principle for sickness that have been tried and tested have had some success, even if not perfect success. If the insurance principle is applied to a homogeneous group like the students in a school, college or university, it is apt to work well, although by no means perfectly and not always smoothly. In a homogeneous unit, such as a lumber camp or a mining community, the principle seems to work on the whole fairly well, but it is impossible to generalize because local conditions defy all generalities. Then, too, any lack of homogeneity is always disturbing. For example, the inclusion of families in the operation of the plan makes for difficulties. Again, it is one thing when there is no medical competition nearby, and another thing if there is an existing community with other industries and other forms of medical care. Certain communities with a fairly common interest, however, are being well looked after medically by homogeneous groups of doctors on an insurance plan suited to the particular circumstances. As a further illustration of what I mean by the homogeneous factor in the insurance principle and the difficulties in the lack of an adequate definition of sickness, I shall cite the example of the Blue Cross. Now, the Blue Cross concerns itself only with hospitalization. It excludes chronic illness and certain diseases. It pays or helps to pay the hospital rates in obstetrics, in acute illnesses like pneumonia, in the hospitalization of fractures and in surgical operations for acute conditions. It is popular because it helps pay for the acute catastrophic emergencies. It does not pay doctors' bills — sometimes, I fear, to the surprise and disappointment of the subscribers. It does not pay for sickness outside the

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as the Golden Rule. Indeed, its application to insurance is not new. At one time, lodge doctors were common. The medical benefits were bait to attract members, and perhaps also a red herring across the trail of masculine social gatherings for the deception of the wife. Young doctors and unsuccessful ones took the jobs of lodge doctors as a possible introduction to practice. They were not paid much, and as a rule they rendered very little and very unsatisfactory service. Indeed, it was sometimes a degradation to depend exclusively on the lodge doctor, to "die to him," as we say in New England. But he was supposed to be better than nothing for the down-and-outers and the chronic medical tramps with many complaints.

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Experimentation has gone even farther. Already various medical groups, notably some of the county medical societies and several of the state medical societies, have sponsored plans for the introduction of medical care in communities, districts, counties and states. These experiments have had many obstacles to overcome and have met with many vicissitudes. As a result of experience at the present time, most plans begin by limiting themselves to obstetrics and surgery — that is to say, sickness that can be more or less explicitly defined. Some of these plans show considerable promise. In any event, they seem to be based on a firmer foundation than the scores of earlier plans under all kinds of auspices that have passed into oblivion. Furthermore, these newer plans, in their pioneering work, test out by trial and error their feasibility and the desires of the public, and they are producing valuable data, including actuarial figures. Some of these plans by affiliation with the Blue Cross are able to furnish complete coverage of hospital and doctors' bills. But, as I have said before, all the problems are not solved. Obviously, a Blue Cross subscriber may prefer hospital residence for a minor operation or a minor illness that might be cared for at home, but he is a subscriber and is entitled to consideration. The hospitals may be overtaxed by this load; indeed, a new type of hospital or hospital wing or ward may be needed. The present "super" hospitals may be too expensive to operate for minor classes of medical illness or of surgery. As you all know, here in this state the Massachusetts Medical Society has fostered and sponsored a plan for state-wide prepayment insurance for low-income groups on a nonprofit basis. Dr. James C. McCann, of Worcester, has borne the heavy burden of inaugurating this plan, called the Blue Shield. The Blue Cross has made generous contribution not only of experience and advice but also of its personnel and organization. A sound and substantial beginning has been made. So far, the Blue Shield accepts only surgical and obstetric cases. To be sure, these are the large catastrophic financial items, if one permits the use of the word "catastrophic" as applied to obstetrics. It is certainly the intent to progress farther into the realm of sickness when experience warrants such a move. Of course, there will be difficulties. Once again the specter of definition raises problems. What is the ceiling — to employ the modern jargon — of low-income groups? And

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One of the products of these activities — or perhaps one of the many stimulating forces — has been the advocacy in some quarters of a universal health-insurance plan on a nationwide scope. There is nothing new about compulsory health insurance, so called. It has been agitated in this country for fifty years at least. In the 1880's Germany adopted a plan of sickness insurance that was carefully studied and that seemed to work well for the Germans, particularly in the case of tuberculosis. The rather sudden drop in the incidence of tuberculosis in all countries irrespective of health insurance and the ability of this country largely to meet this problem on a state or even a smaller unit level seemingly discouraged enthusiasm for such a plan here.

The adoption of compulsory health insurance in the British Isles thirty years ago, however renewed the discussion. Other European countries before and since have adopted varying schemes of compulsory sickness insurance, usually on a nationwide level. The course of compulsory health insurance in Britain has been followed with great interest in this country. Contrary to the expectations and even the promise of its proponents, it has been concerned with sickness and not with health. The public-health activities have been minimized rather than emphasized. The death rate has not been lowered so rapidly as that of the United States. There has been much discussion and much acrimony on both sides of the question and on both sides of the Atlantic. The operation of the British act has not been free from politics; it has not improved medical practice and indeed has been a good deal of a deterrent to the public-health movement. There have been the usual difficulties of all insurance plans. At the present time, changes in the British act are contemplated and are being discussed. The medical profession of Great Britain does not find the act satisfactory but is reluctant to encourage drastic changes that it fears would eventually result in more governmental and political control. It pleads for cautious experimentation and for action only after study of the actuarial data, and for freedom from political manipulations. The medical profession in Great Britain wants clarification of governmental activities in respect to poverty and medical service.



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In other words, the doctors object to the government's giving medical care as a dole to the poor, instead of providing them with the necessities of life — shelter, food, fuel, clothing and so forth. It is necessary, they claim, to separate poverty and the measures used to alleviate poverty from sickness and the measures used to alleviate sickness. Doubtless there is a connection between poverty and illness. One may well be the cause of the other, but poverty is not always the cause of illness. And certainly financial security does not ensure freedom from disease or freedom from worry.

Sir William Beveridge, the well-known British economist, and his plan decidedly stimulated the discussion. If I understand the plan correctly, it is an attempt to show how the insurance principles may be used, primarily against poverty and incidentally against unemployment, old age, the bringing up of children and so forth, including illness. Sir William recognizes five giants of evil — want, disease, ignorance, squalor and idleness. He claims that want or poverty is probably the easiest to attack. His plan is focused primarily on poverty and incidentally on sickness. He does not himself seem to have any opinion about its workability. Indeed, in a lecture in London some years ago he declared that it was not the business of the professional economist to develop legislation to any end. I believe, however, that Sir William has recently been elected to Parliament, so he may have changed his mind. Then, being an Englishman, he is a bit hazy on the role of hospitals in illness. One of the proponents of the federal compulsory-insurance law in the United States wrote to me that it did seem that Sir William was rather vague on the subject of hospitals. In the United States, of course, the hospital is on the front line in the battle against illness. In any case, it is difficult or impossible to transfer the experience of one country to another. Even in Great Britain, the Compulsory Insurance Act in a number of respects is different in Scotland from what it is in England, although both countries are on the same relatively small island. The people of England and Scotland together are decidedly more homogeneous than the people in this vast country. The British have no Negro problem, for example. They have an Indian problem, to be sure, but not in the British Isles. Medical education in Great Britain is vastly different from that in the United States. The whole system of medical practice is different. The British still talk of nursing homes instead of private hospitals. Their nursing service is generally considered to be inadequate. Of course, I should hasten to say that the best of medical science and of medical practice in the British Isles is as good as that anywhere in the world, but the top-flight men are relatively few. In the United States, many of the rank and file of the profession are close to the top, which is certainly not the case in England.

Certainly at one time during the last thirty years the medical profession and the British Medical Association seemingly accepted the plan of compulsory health insurance; perhaps passive resignation to the act is more accurate phraseology. But more recently vigorous objection is being voiced. A Scottish physician entirely unconsciously illustrated some of the drawbacks and weaknesses of the act when he assured me that he liked the plan. The reason he gave was that after years of hard work the doctor had something that he could sell when and if he was minded to retire. Naturally, I asked him if a physician could turn over his panel patients in that fashion. Of course, said he, if one stood in well with the administrator, who ordinarily is not a doctor. I did not think it was appropriate to ask how one stood in well with the administrator, but did venture to ask about the application of the principle of freedom of choice on the part of the panel patients. He put me in my place emphatically and profanely for my visionary foolishness in regard to this, and in regard to my next query which concerned what would happen if the purchaser proved to be incompetent.

The Scottish physician was a man of some importance in his community and in the profession. His remarks were sadly substantiated by other physicians, who, as doctors are wont to do, retailed their own pet grievances. A common grievance was that the administrator was often arbitrary in refusing approval of expensive drugs. As we all know, some doctors prescribe preparations of drugs that are expensive when inexpensive preparations may be just as good or even identical. I got the impression, however, that there was a substantial reason for the grievance.

The big frogs in the medical puddle — that is, consultants on Harley and Wimpole streets in London and their prototypes in smaller centers — find that they derive a considerable consultation practice rather directly from this panel system. The panel physician sees the patients in his surgery, but if the patient desires or needs even a routine examination, too often he has to get it at his own expense from the consultant.

My best guess is that, by and large, the doctors in Great Britain benefit financially by this system. It is to be noted that the system was not inaugurated by the doctors. From it has developed what seems to be a sorry state of affairs for the patient and for medical standards of practice.

I have dwelt on the British experience with compulsory insurance because it is so much in the discussion, as well as because it shows clearly some of the fundamental difficulties in a nationwide plan. On the state level or lower, the same and additional difficulties have been discovered in this country. I believe that if the whole subject of compulsory insurance for sickness were better understood, possibly more profitable progress might be made. It

Certainly at one time during the last thirty years the medical profession and the British Medical Association seemingly accepted the plan of compulsory health insurance; perhaps passive resignation to the act is more accurate phraseology. But more recently vigorous objection is being voiced. A Scottish physician entirely unconsciously illustrated some of the drawbacks and weaknesses of the act when he assured me that he liked the plan. The reason he gave was that after years of hard work the doctor had something that he could sell when and if he was minded to retire. Naturally, I asked him if a physician could turn over his panel patients in that fashion. Of course, said he, if one stood in well with the administrator, who ordinarily is not a doctor. I did not think it was appropriate to ask how one stood in well with the administrator, but did venture to ask about the application of the principle of freedom of choice on the part of the panel patients. He put me in my place emphatically and profanely for my visionary foolishness in regard to this, and in regard to my next query which concerned what would happen if the purchaser proved to be incompetent.

The Scottish physician was a man of some importance in his community and in the profession. His remarks were sadly substantiated by other physicians, who, as doctors are wont to do, retailed their own pet grievances. A common grievance was that the administrator was often arbitrary in refusing approval of expensive drugs. As we all know, some doctors prescribe preparations of drugs that are expensive when inexpensive preparations may be just as good or even identical. I got the impression, however, that there was a substantial reason for the grievance.

The big frogs in the medical puddle—that is, consultants on Harley and Wimpole streets in London and their prototypes in smaller centers—find that they derive a considerable consultancy practice rather directly from this panel system. The panel physician sees the patients in his surgery, but if the patient desires or needs even a routine examination, too often he has to get it at his own expense from the consultant.

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In other words, the doctors object to the government's giving medical care as a dole to the poor, instead of providing them with the necessities of life—shelter, food, fuel, clothing and so forth. It is necessary, they claim, to separate poverty and the measures used to alleviate poverty from sickness and the measures used to alleviate sickness. Doubtless there is a connection between poverty and illness. One may well be the cause of the other, but poverty is not always the cause of illness. And certainly financial security does not ensure freedom from disease or freedom from worry.

Sir William Beveridge, the well-known British economist, and his plan decidedly stimulated the discussion. If I understand the plan correctly, it is an attempt to show how the insurance principles may be used, primarily against poverty and incidentally against unemployment, old age, the bringing up of children and so forth, including illness. Sir William recognizes five giants of evil—want, disease, ignorance, squalor and idleness. He claims that want or poverty is probably the easiest to attack. His plan is focused primarily on poverty and incidentally on sickness. He does not himself seem to have any opinion about its workability. Indeed, in a lecture in London some years ago he declared that it was not the business of the professional economist to develop legislation to any end. I believe, however, that Sir William has recently been elected to Parliament, so he may have changed his mind. Then, being an Englishman, he is a bit hazy on the role of hospitals in illness. One of the proponents of the federal compulsory-insurance law in the United States wrote to me that it did seem that Sir William was rather vague on the subject of hospitals. In the United States, of course, the hospital is on the front line in the battle against illness. In any case, it is difficult or impossible to transfer the experience of one country to another. Even in Great Britain, the Compulsory Insurance Act in a number of respects is different in Scotland from what it is in England, although both countries are on the same relatively small island. The people of England and Scotland together are decidedly more homogeneous than the people in this vast country. The British have no Negro problem, for example. They have an Indian problem, to be sure, but not in the British Isles. Medical education in Great Britain is vastly different from that in the United States. The whole system of medical practice is different. The British still talk of nursing homes instead of private hospitals. Their nursing service is generally considered to be inadequate. Of course, I should hasten to say that the best of medical science and of medical practice in the British Isles is as good as that anywhere in the world, but the top-flight men are relatively few. In the United States, many of the rank and file of the profession are close to the top, which is certainly not the case in England.

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is painful to report that many doctors have little basic information on the topic. Too often some doctors express very emotionally their prejudices against what they regard as interference with the present system of medicine, which beyond doubt is the most effective in the world, but which is far from perfect and which can and should be improved, particularly so far as distribution of medical service is concerned. At times, the doctors are so vehement that they are charged with selfish interest. On the other hand, the average citizen thinks of his own selfish interest. He is, as a rule, interested mainly in good medical care, to be sure, but also at the lowest financial rate. The patient naturally wonders whether the insurance plan will not help his pocket-book. When the discussion becomes acute or acrimonious, the character of medical service gets lost. Thoughtful persons are properly much concerned over the quality of medical service. To me this is the nub of the whole matter, and I believe that this is the view of the substantial proportion of the medical profession. Changes will and must go on in the future. They have in the past. Anyone who thinks back, not thirty years but ten years, is acutely conscious of change. Certainly any doctor active in practice is aware of his own role in the change in medical practice. Otherwise, he would not be active in practice. I say this with the full conviction that the doctor is not sacrosanct and not even master of his own destiny. He is peculiarly a product and a creature of the community. The doctor does not want to dominate or dictate. He could not if he would. He is, however, the expert witness in the case. In the meantime, experimentation must and will continue. It is unthinkable that without careful study of the difficulties as actually encountered any revolutionary change will be adopted. Thinking is needed more than emotional slogans in which words do not mean what they ought to mean.

Personally, I am in favor of a broad, vigorous attack on poverty and want. Old age and unemployment must be faced and provision must be made for them. But mark you this, and to me the difference is vital, a pension is given to the elderly and a cash benefit to the unemployed, but in the case of illness in federal compulsory-insurance plans, medical service, not cash, is to be furnished through the government to the sick. Why this curious distinction, and why not keep separate, so far as possible, poverty and illness? And what if a government undertook not to supply cash to old age or for unemployment but to utilize the same principle as suggested for medical service? Would it be old age homes, or else, or particular jobs for the unemployed, or else? Is the question real or rhetorical, and why?

Poverty and want exist in the United States, even if they are not so horribly conspicuous as in Britain. And in no country does the attempted control of

poverty and want include that social misfit so accurately described by Prime Minister Churchill as the "pub crawler." In America, he is the "bar-room bum."

Since we have the Social Security Act in this country, I see no reason for the exemption of those employed in educational and religious institutions and in hospitals. My personal concern, as I have said before, is the quality of medical service, which must always be rising to higher and higher standards to ensure a healthy and happy people.

Certainly one must appreciate as an illustration the phenomenal growth of private insurance in the United States. There are now more than eighteen thousand industrial firms that are covered, with more than twenty million policyholders. They are covered, in most instances, with hospitalization, a \$10 weekly disability allowance, \$100 to \$150 for surgical fees and an allowance for laboratory and x-ray charges. One medical society is arranging with an insurance company to cover everybody in the county in groups of five or more people.

Given reasonable opportunity, it seems likely that private insurance can do the job better in the United States than can the federal government.

Within the seemingly visible future, the war for freedom will be won. Paradoxically, to win this freedom we have had to sacrifice some of our own freedom. This we have done gladly and cheerfully for the cause. After the cessation of armed hostilities we shall have another freedom to win. We shall be tired; we shall be used to regimentation and to bureaucratic regulation of this and that. But I believe that we shall win back that freedom too. I believe that there is enough intelligence, enough imagination, enough initiative, enough resourcefulness and enough resolute determination to solve in our own American way these problems that I have discussed tonight. I believe that only dull and weary people turn their problems and troubles, with their freedom, over to others, which is in this case the government.

We may or may not like the lesson, but the glorious youth of this country has taught us of the older generation that too often what we thought was parental interest and solicitude was actually to their view paternalism, even if friendly, and at times a form of despotism even if benevolent in design. They want freedom, not paternalism or despotism, and we must give it to them, albeit with a prayer that they do not confuse license and liberty.

Once more I want to state with all the emphasis that I possess that this country needs better medicine. In improving medical service, the problems of better distribution must and will be solved. But let us not forget that we still need better doctors and better medical practice.

## THE McMURRAY OSTEOTOMY FOR NONUNITED HIP FRACTURES\*

OTTO J. HERMANN, M.D.†

BOSTON

IN OCTOBER, 1939, I<sup>1</sup> reported on a small series of hip reconstructions done for painful, non-united fractures of the femoral neck under the various prevalent standard procedures. These included the Colonna modification<sup>2</sup> of the Whitman method, the Magnuson modification<sup>3</sup> of the Brackett operation, direct bone graft and hip fusion.

On the whole, the percentage of good end results was discouraging, except, perhaps, for those obtained from the hip-fusion method. The temptation to adopt this procedure as the one of general choice was great, but I believed that it should not be done. After reading McMurray's<sup>4</sup> paper on fractures of the neck of the femur treated by oblique osteotomy, I was eager to try out his method on some painful nonunited hip fractures. At about that time, however, a discouraging talk with two surgeons from across the Atlantic on the ultimate (three-year) end results deflected me temporarily from going ahead with McMurray's osteotomy treatment. Some time later, after thinking over the reports of McMurray<sup>4</sup> and others of the high percentage of successful end results following such osteotomies, giving a high degree of painless hip function, which was nearly normal in many cases, I began doing the McMurray type of oblique osteotomy in a few selected cases of painful nonunited hip fractures. For two years the following McMurray technic, as described by me<sup>1</sup> in 1939, was used.

The McMurray osteotomy . . . is a bifurcation operation based on the suggestion of Lorenz in which the shaft of the femur is transferred directly under the lower margin of the acetabulum and head of the femur. The chief purpose of this operation is to change a shearing force into a direct one. The following are the steps in this operation:

A 15-cm. incision is made along the lateral side of the upper end of the femur in the trochanteric area. The fracture site is exposed so as to place the osteotomy line accurately. An oblique osteotomy is performed beginning on the outer side of the shaft, generally about the lower end of the greater trochanter and ending above the tip of the lesser trochanter. The upper end of the shaft of the femur is pried and shoved inward until the cut end is under the acetabulum and femoral head. This is followed by repair of the wound. A plaster-of-Paris fixation is used for a period long enough to ensure union at the site of the osteotomy. This fixation of the limb is in the neutral position in very slight abduction in order to prevent the development of knock-knee following removal of the plaster cast. Fixation is maintained generally three and a half to four months. The knee is kept in slight flexion so that the degree of rigidity is decreased.

In September, 1941, I<sup>5</sup> reported, besides other types, 8 nonunited hip fractures treated by McMurray's procedure. Six of them had progressed, as I thought, long enough to give a fair evaluation of their end results. At that time I wrote:

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 24, 1944.

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Five of the 6 cases have gone clinically to good end results, and 1 patient, although not an absolute failure, still has to use crutches after six months. . . . In the few cases done by this method at our hospital the following data have been gathered: the patients have plaster-of-Paris spica fixation from eight to fourteen weeks, and hospitalization from ten to about seventeen weeks; they generally leave the hospital using crutches but soon thereafter omit them and use only a cane, with good clinical end results; they still use a cane in going upstairs, limp slightly, but have no local hip pain or tenderness on walking, sitting or lying down; the shortening varies from 2.2 to 2.6 cm.; there is a limited degree of internal, but a good degree of external rotation at the reconstructed hip, and also a good abduction and adduction range; there may be occasional stiffness; the patients can dress themselves in normal fashion, cross their knees and sit for protracted periods with ease and comfort. In short, a good 80 to 85 per cent return to normalcy is usually obtained. . . .

At present the McMurray osteotomy seems adaptable to a greater variety of the painful nonunited femoral-neck fractures than the other methods. The other points in its favor are its simplicity of execution, the production of less surgical shock and, lastly, the fairly high rate of good end results showing a very creditable percentage of return to normalcy.

Since the publication of this report, 11 more such reconstructions have been done at the Boston City Hospital by various surgeons. Two modifications in the technic were added. First, to place the osteotomy line more accurately a Kirschner wire is inserted in the proposed osteotomy line and its position is checked by x-ray, the wire then being used as a guide in doing the actual osteotomy. Second, in several cases the Blount blade plate has been used as a means of internal fixation after the osteotomy has been done. The first modification served to place the osteotomy much more accurately than the ordinary touch method, and the second was a definite improvement in that it was possible to do away with the prolonged plaster-of-Paris spica fixation and bed confinement, and it also prevented the cut end of the distal femoral shaft from slipping or sliding out.

Five of the 8 cases reported in 1941 have been re-examined. In all of them the 1941 end results had been deemed successful. Two patients have developed considerable pain, have lost some of their local hip-motion range, and show an increase in shortening because of some change in position of the distal femoral shaft due to lack of real bony union. Thus, the 1941 rating of the McMurray osteotomy has had to be revised downward.

Of the last 11 patients treated, 2 died soon after the operation, one three days afterward from cerebral thrombosis, and the other within twenty-four hours from cardiac failure. These 11 cases have been summarized as follows:

CASE 1. L. S., a 51-year-old woman, received on 1943, a McMurray osteotomy for a painful nonunion of the right femoral neck in which the pi



Kirschner-wire technic was adopted. A plaster-of-Paris spica fixation was used, with the leg in 20° abduction and in the neutral position, until September 24. The patient was discharged on October 3 on crutches. She discarded them on October 10 and used a cane until December 25. She now limps somewhat but can do her daily routine walking. She can sit with complete comfort for several hours, although the leg stiffens temporarily after 1½ hours of sitting. There is some soreness of the hip at night and during inclement weather. She can go up and down stairs one step at a time using a cane. A recent physical examination revealed a 3-cm. shortening of the right leg. The internal rotation was practically nil and the external rotation 20°. Adduction was limited to 15°, and abduction to 25°. The quadriceps muscle group showed some atrophy. The patient had some difficulty in putting on her stocking and shoe.

*Comment.* This case does not show an 80 or 85 per cent return to normalcy, but the patient has an almost painlessly functioning hip and can do her routine daily walking and sitting, neither of which was possible before the osteotomy.

CASE 2. J. DeL., a 51-year-old man, received on March 3, 1943, a McMurray oblique osteotomy followed by a Blount internal blade-plate fixation. He left the hospital on crutches on April 6, and the crutches were discarded in July. Since then the patient has used a cane or one crutch. He was non-co-operative, and it was difficult to convince him that daily routine leg exercises and walking were important to his progress. He now does more walking but has recurring pain in the hip when tired. He can, however, sit with comfort and can put on his sock and shoe without much difficulty. The leg presents a 3-cm. shortening with only slight internal rotation. Adduction is limited to 15° and abduction to 30°. Flexion at the thigh is 35°. The patient goes up and down stairs with the aid of the railing or a cane.

*Comment.* This patient can at least walk and sit with a fair degree of comfort and can dress himself, neither of which was possible previous to the osteotomy. Although there is recurring pain on tiring after long walks, it ceases after a short rest and is thus not so severe and persistent as before the operation.

CASE 3. E. C., a 76-year-old woman, received on September 23, 1942, a McMurray osteotomy for a painful, non-functioning, nonunited fracture of the right hip. A plaster-of-Paris spica fixation was used for 3 months. The patient was discharged on January 8, 1943, using crutches with active weight bearing. She discarded one crutch on February 1, used the other for another month, and has since been using a cane. She had complete relief of pain for 5 months following the operation, but at present has some pain in the hip and knee, which is relieved by acetylsalicylic acid. She does her normal amount of daily walking, goes to the motion pictures and sits for several hours with comfort, does her daily housework and can easily put on her shoe and stocking. She does, however, limp somewhat and still uses a cane. The right leg shows a 3-cm. shortening. There is limited internal rotation at the right hip but 40° of external rotation. Adduction is limited to 15° and abduction to 25°. There is 15° flexion deformity. The patient walks with the right leg in some degree of external rotation.

*Comment.* This can be considered a fair end result only in that the patient can walk, sit and dress herself with a fair degree of ease and do her daily housework, none of which could be done before the operation.

CASE 4. M. M., a 50-year-old woman, received a McMurray osteotomy on May 20, 1942. A plaster-of-Paris spica was applied for 13 weeks. The patient was discharged on August 17 on crutches, used them until July, 1943, then discarding them for a cane. At present she is doing a moderate amount of walking. She returned to her work as a telephone operator in the summer of 1943. She can sit with comfort. The only pain she has in her hip is of moderate degree and appears — strangely enough — on arising in the morning. The leg presents a 2.5-cm. shortening. Adduction is limited to 20° and abduction to 25°. There is internal rotation of only a few degrees, but external rotation of 45°. There is a flexion deformity of 15°, with further flexion to 90°.

*Comment.* This patient progressed slowly — owing to her apprehensive attitude — to a reasonably good end result. She

walks well with the aid of a cane, and can sit with ease for protracted periods, as her work attests. She still has difficulty in putting on her shoe and stocking. She could not walk or sit with comfort previous to the operation.

CASE 5. E. W., a 62-year-old woman, received a McMurray oblique osteotomy for painful nonunion of a fracture of the left hip on October 23, 1942. A plaster-of-Paris spica was applied. This operation was done under intravenous Pentothal Sodium anesthesia. The patient showed no unfavorable immediate postoperative reaction, but 3 days later died from cerebral thrombosis.

CASE 6. N. J., a 65-year-old woman, received a McMurray osteotomy on February 12, 1942, after having been treated medically for arteriosclerotic disease. She was considered a fair risk for the osteotomy, but died 24 hours post-operatively from cardiac failure.

*Comment.* Although the patient in Case 5 appeared to be an excellent operative risk, Case 6 was of the borderline type, preoperative medication being necessary for over a month. It would probably have been better judgment to let this patient remain a wheel-chair invalid.

CASE 7. J. P., a 62-year-old man, received a McMurray osteotomy for the left femur on February 20, 1942. A plaster-of-Paris spica fixation was used for 3 months. The patient was discharged on June 1, using crutches. He is now up and about using a cane. He can walk with comfort, has no hip pain and gets about much better than before. He cannot cross the left knee over the right, but he can put on his sock and shoe. He can go up and down stairs using the banister and a cane. The leg presents a 3-cm. shortening. There is practically no internal rotation at the hip, but there is external rotation of 25°. Adduction is limited to 20° and abduction to 25°. There is a 10° flexion deformity, with further flexion to 70°.

CASE 8. J. McG., a 69-year-old man, received on November 11, 1941, a McMurray osteotomy for a nonunited fracture of the left femoral neck, performed by the preliminary Kirschner-wire technic. A plaster-of-Paris spica fixation was applied until January 16, 1942. Because of some stiffness of the left knee, he was put on balanced traction. On February 11, he started using crutches, and 1 week later he was discharged on crutches. He gave them up in March, 1942, and used a cane, which he still uses when walking out-of-doors. He can walk and sit with comfort, although prolonged sitting causes some local stiffness but no pain in the hip. There is occasional pain in the knee, and he limps when walking. This has now been greatly decreased by inserting a lift in the shoe. There is a 3-cm. shortening of the leg, a few degrees of internal rotation — under 5° — 35° of external rotation, 25° adduction, and 30° abduction. There is some quadriceps atrophy.

*Comment.* This patient not only had a painful hip condition before November, 1941, but also had a bothersome left knee that became quite stiff following the spica fixation. This knee still gives him some bother on prolonged sitting or after long walks. The hip is comfortable considering the degree of motion and amount of shortening. This result cannot be considered a return to 80 per cent normalcy, but the patient has a serviceable, painlessly functioning hip.

CASE 9. V. S., a 72-year-old man, received on September 17, 1943, a McMurray osteotomy for a painful nonunited fracture of the left femur, which was followed by a Blount blade-plate fixation. The patient suffered severe post-operative shock and had to have plasma and later two blood transfusions. An adductor tenotomy was done on October 1. The patient was discharged on December 9, using crutches. He gave up the crutches for a cane in January, 1944. He does not take long walks but when walking has no hip pain. He tires easily but can sit for protracted periods without pain. He can put on his sock and shoe easily. The leg presents 2.5-cm. shortening. There are a few degrees of internal rotation, and 35° of external rotation. Adduction is limited to 15° and abduction to 25°. There is no hip pain on the push-and-pull test.

*Comment.* This patient has attained a painlessly functioning hip, can walk and sit and dress himself with comfort and



has no hip pain. He is gaining strength and can take longer and longer walks.

**CASE 10.** J. F., a 66-year-old man, received on September 14, 1943, a McMurray osteotomy, followed by a Blount blade-plate fixation. He sat up on September 29 and walked on crutches on October 10. He was discharged on October 23 using crutches. He is still using crutches although he has some pain on protracted sitting or walking. Extreme cold gives him some local discomfort. He has done none of the daily prescribed simple exercises and cannot be persuaded to discard his crutches for a cane. He cannot put on his sock and shoe. The leg presents considerable disuse atrophy. There is practically no degree of internal rotation at the hip. The external rotation is 25°. Adduction is limited to 10°, and abduction to 30°. There is a flexion deformity of 15°. There is some pain in the hip on the push-and-pull test and on any attempt at forced rotation.

*Comment.* This patient, although walking for short distances, is still using crutches. He can sit with comfort for a short while but finds that long sitting causes hip pain. He also cannot dress himself. This is not a good end result.

**CASE 11.** J. R., a 64-year-old woman, received a McMurray osteotomy on July 10, 1942, followed by spica cast fixation until September 10. On its removal, the left-knee flexion was 30°. She walked with crutches until January, 1943, and then used a cane. At present, she uses a cane occasionally and wears a 2-cm. lift in her shoe. She has no hip pain. She did have some pain in the knee and hip on getting out of the spica, but persistent local physical therapy in the form of massage, exercises and heat, limbered up the leg so that by January, 1943, she was walking with comfort using a cane. She now does her own housework and her normal daily walking, sits with comfort, can cross her knees and dress herself and can go up and down stairs one step at a time. The leg presents a 3-cm. shortening. Abduction is limited to 25°, and adduction to 15°. There is practically no internal rotation but a good degree of external rotation. On the push-and-pull test there is no "give" or pain in the hip.

*Comment.* This patient finally had an excellent end result after a discouraging immediate postoperative convalescence, due chiefly to her knee.

From this series and the previously reported one, the following composite data have been gathered.

The preliminary Kirschner-wire insertion through the proposed osteotomy site, together with an immediate x-ray checkup as a guide for the osteotomy, is extremely valuable, even though it consumes an extra five minutes. It serves to place the osteotomy more accurately than does the sight-and-touch method.

From the cases treated postoperatively by the plaster-of-Paris spica fixation the following points are deduced: Despite the apparent simplicity and shortness of the operation itself, the high mortality figure shows clearly that a good deal of shock is entailed and that the patients must be chosen as carefully as for the other, more surgically devastating, reconstruction procedures. The cases chosen are those deemed good surgical risks by both the surgeon and the internist. These patients must be given good supportive treatment before and after the operation, especially those in spica fixation, who require a bed-rest period of eight to fourteen weeks, with a few more additional weeks of hospitalization. These patients as a rule leave the hospital on crutches and discard them in periods varying from a week to a year, depending on the local condition and the co-operation of the patient. Those who come to a good clinical end result following this

method — one can expect about 80 per cent to do so — walk with a slight limp owing to the resultant shortening of 2 to 3 cm. They do their daily amount of routine walking and go up and down stairs without pain but using a cane. Some have moderate pain at the end of a day after an extra-long walk. They can sit and lie with comfort, although in some cases there is a feeling of local stiffness on getting up after a protracted sitting, which, however, passes off on moving about. They can as a rule put on the stocking and shoe on the affected leg because they can flex the hip and cross the knees and adduct and externally rotate the leg. It is true that the crossing of the legs is often done with some difficulty but there is no pain. The patients can brace themselves on their legs quite well because of the presence of an average of 25 to 35° of abduction. From a local anatomic standpoint the picture is not encouraging, and all that can be said is that the form shearing force of the femur has been transposed into a direct force that eliminates pain and gives sufficient stability and mobility at the hip joint to enable the patient to go about in a good degree of functioning comfort with the aid of a cane.

The several cases in which the Blount blade-plate internal fixation was used following the osteotomy furnished additional data. The technique part of the fixation could be made much simpler and the plate made to conform more accurately to the angular shape needed if a two-piece combination, such as the Thornton plate together with the Smith-Petersen nail, was used. This fixation does away with postoperative spica fixation and thereby allows much earlier mobility of the various joints involved in the spica fixation and, of course, much earlier application of local physical therapy. It shortens the bed-confinement period by five to eleven weeks. The final advantage of this fixation is that it prevents the slipping or sliding of the transposed femoral shaft from its moorings.

#### SUMMARY AND CONCLUSIONS

The McMurray osteotomy is not so simple and nonshock-producing as originally thought.

The cases chosen for the operation should be selected carefully from a local and general standpoint. There must be a fairly viable head and some femoral neck, and the patient must be a good surgical risk.

The patients should receive definite well-guided preoperative and postoperative physical therapy and general supportive medication and nutrition as outlined by the medical consultant. As the postoperative period goes into the third year or more, there may be a return of hip pain, owing to local changes in position or to bony changes. A good end result by this method gives a painlessly functioning hip, enabling the patient to sit, walk and dress with comfort. This means a great deal to a patient who

previous to the operation was having persistent local hip pain and was confined to a bed or wheel chair or compelled to use crutches. The McMurray operation, although apparently more generally adaptable than other methods, for the reconstruction of painful nonunited hips and of easier execution, and probably giving a higher percentage of painlessly functioning hips, should not be universally used in such cases. Now, as always, the surgeon ex-

perienced in such procedures should choose the one he considers best adapted to the case in hand.

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## VAGINAL BLEEDING FROM POTASSIUM PERMANGANATE AS AN ABORTIFACIENT

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**B**URNS of the vagina and cervix due to the use of potassium permanganate tablets as an abortifacient constitute a new and gradually increasing serious complication of early pregnancy in and around Boston. Since March, 1936, when this diagnosis was first made at the Boston City Hospital, 65 cases have been treated by the Gynecological Service. Inasmuch as this entity has been so infrequently mentioned in the literature, it is the purpose of this paper to present its important features and the report of a case with serious sequelae.

A review of the literature reveals that there has been only one article written in English on this subject.<sup>1</sup> Between 1932 and 1940 twelve articles were written in Italian and Spanish on the use of potassium permanganate solution as a vaginal medicant.<sup>2-13</sup> These papers mention the use of potassium permanganate tablets as an abortifacient.

A review of the records of the Gynecological Service shows that from 1936, when 3 cases were admitted, to the present there has been a gradual increase in the number of admissions for this type of case, 20 cases having been admitted in 1943. From January 1, 1930, to January 1, 1944, 15,976 cases of all types were admitted to this service. There were 65 patients with potassium permanganate burns of the vagina or cervix, representing 0.4 per cent of all admissions. During the years 1941 to 1943 these cases comprised 5 per cent of the patients admitted with threatened miscarriages.

The ages of these 65 patients varied from eighteen to thirty-eight years. There were 36 patients in the third decade, 19 in the fourth, and 9 in the second. Of the 53 patients who were multiparas, 38 had been delivered of living babies within the year previous to the date of admission to the hospital, and they all offered this as the reason for attempting to produce an abortion.

Forty-two of the patients had missed only one monthly period. The duration of the amenorrhea

in the remaining cases was as follows: two months, 14 cases; three months, 5 cases; four months, 2 cases; and five and six months, 1 case each.

No patient was ever sent to this service with the diagnosis already made. The diagnosis of the admitting physician was usually threatened miscarriage. Each patient gave a history of some menstrual irregularity, but finally admitted having inserted a "tablet" to bring on an overdue menstrual period. The usual history was that of spontaneous, painless bleeding. Eighteen patients complained of irregular bleeding for several months. The histories as given by the patients suggested all the various causes of vaginal bleeding that might be found in this age group.

Questioning concerning artificial induction of bleeding in all cases of vaginal hemorrhage is a routine matter at the time of admission, and it was only in replying to this query that 22 patients admitted using potassium permanganate. The other 43 denied the use of any method of induction, and it was only after vaginal examination and detection of the lesion that they admitted using this chemical as an abortifacient.

The onset of bleeding usually occurred within two hours of the time that the tablet was inserted.

The diagnosis is indicated by profuse bright-red bleeding, with persistence of fresh bleeding after removal of the vaginal clots. In most cases the irregularity caused by the chemical burn can be felt on the cervix or on the vaginal mucosa. Speculum examination, which is not a routine procedure in the examination of patients with threatened miscarriage on this service, reveals one or more eroded areas covered by a black eschar that are usually found in the posterior fornix on both the cervix and the vaginal mucosa. When this lesion is found on the cervix without an eschar, it resembles a severe cervical erosion or carcinomatous crater. The bleeding varies from a slow ooze to a bright-red arterial pulsating flow.

In 4 cases in which a speculum examination did not seem indicated, a diagnosis of incomplete mis-

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carriage was made because of the seemingly open cervical os and the misleading history of having passed fetal tissue. These patients were prepared for dilatation and curettage, and it was only after the cervix was exposed under general anesthesia that the correct diagnosis was made.

A diagnosis of pregnancy based on physical findings was made in 40 cases. In the remaining cases either the patient was not pregnant or there was not sufficient evidence to make the diagnosis.

In 10 cases it was necessary to treat the patient in the operating room, where, under general anesthesia, one to three mattress sutures were placed about the bleeding points. Thirty-four cases were treated by firmly packing the vagina for forty-eight hours. Twelve cases required rigid shock treatment, including several transfusions.

Only 6 patients were successful in producing an abortion, as evidenced by the recovery of fetal tissue. One of these patients returned when her menstrual period was overdue for a second time and admitted that she had inserted two tablets of potassium permanganate on the previous day.

The average hospital stay was five days. There were no deaths. There was no evidence of generalized toxic symptoms as the result of absorption of this chemical.

#### CASE REPORT

S.R., a 34-year-old tripara, was admitted with a chief complaint of vaginal bleeding. Her last menstrual period had occurred on May 11. She stated that for 6 weeks she had had slight staining, using a pad a day. She was well on going to bed the night before admission, but after having intercourse began to bleed profusely. She felt weak and fainted and was brought to the hospital in shock. She denied induction. The blood pressure was 70/30, the pulse 140, and the respirations 25.

There had been two full-term normal deliveries and one miscarriage. The last pregnancy occurred 12 months previously, and terminated in a miscarriage in the 3rd month.

Vaginal examination showed parous introitus and large blood clots in the vagina. The cervix was soft. The cervical os was closed. The uterus was the size of a 4-month pregnancy. The vaults were free. There was an irregularity of the posterior lip of cervix, extending into the vagina. Speculum examination revealed a moderate amount of blood in the vagina. On removal of the clot there was bright-red bleeding from a crater the size of a half dollar on the posterior lip of the cervix and extending into the posterior fornix.

The patient was brought to the operating room, and under nitrous oxide and oxygen anesthesia three mattress sutures were placed in the posterior lip of the cervix and a firm pack was placed in the vagina and left in place for 48 hours. The patient was transfused and treated for shock for several hours, with eventual recovery. She was discharged on the 7th hospital day.

The patient was followed in the Prenatal Clinic throughout the ensuing months of her pregnancy. It was noted that the cervix was gradually becoming distorted as a result of a cicatrix. The cervix pointed posteriorly and was continuous

with the cicatricial mass, which replaced the posterior fornix. Since the cervix was hard, and since the os was only a little larger than a pinpoint, a cesarean section was done at term.

Owing to the gradually increasing frequency of this relatively new entity, physicians, particularly those practicing in and about Boston, should consider it in a differential diagnosis of all cases of vaginal bleeding in the childbearing age. It is doubly important when one considers that in all these 65 cases not one patient gave an accurate history. As a result of the wrong diagnosis these cases may be improperly treated as threatened miscarriages and pregnancies may be unnecessarily interrupted.

There may be some significance in the fact that the first appearance of this entity in the foreign literature occurred shortly before the first case was seen at the Boston City Hospital. The patients were extremely reluctant to give the source of their fallacious information, and were surprised when they were told that potassium permanganate was not an abortifacient. It seems that an attempt should be made to educate the laity about this fallacy before use of the drug becomes more widespread.

#### SUMMARY

A series of 65 cases of vaginal bleeding following the use of potassium permanganate as an abortifacient is presented, and a typical case is reported.

The importance of this drug as a cause of vaginal bleeding during early pregnancy and the dangers of improper treatment based on an incorrect diagnosis are emphasized.

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## MEDICAL PROGRESS

### PHYSICAL MEDICINE IN REHABILITATION

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REHABILITATION has been defined as the planned attempt through the use of all recognized measures under skilled direction to restore those persons who, because of disabilities, do not assume to the greatest possible extent and at the earliest possible time that place in the productive system of society that they are potentially capable of assuming.<sup>1</sup> Physical medicine, which includes physical and occupational therapy, is an important adjunct to ordinary medical and surgical treatment in rehabilitation, particularly in wartime. Krusen<sup>2</sup> has reported that in civilian practice 5 to 10 per cent of all patients require some form of physical treatment. At the Mayo Clinic 8.3 per cent of all the patients who registered in 1939 were treated in the Section on Physical Medicine. In 1942 the proportion increased to 9.5 per cent. In military practice the percentage of patients who require physical rehabilitation is considerably greater. In several army hospitals 20 to 30 per cent of all patients are referred for physical therapy. As further evidence of the magnitude of these problems, it has been estimated that in 1942 there were 4,000,000 persons in the United States who suffered from physical impairment and that the annual increment was 800,000.<sup>3</sup> Two hundred and sixty thousand of these were said to need some type of rehabilitation and 50,000 were in the process.

An over-all view of rehabilitation in various types of disorders is shown in a table in the appendix to the Tomlinson<sup>4</sup> report, which was reprinted in a paper by Krusen.<sup>5</sup> By referring to this table it can be seen that physical and occupational therapy have a large role in any rehabilitation scheme.

Rehabilitation is a popular topic, and many papers have been written recently on the sociologic, economic and medical aspects of the subject. One of the first books to appear was a symposium entitled *Rehabilitation of the War Injured*, edited by Doherty and Runes.<sup>6</sup> Here can be found authoritative articles by an impressive group of experts giving short summaries of procedures and methods that are of value. Medical, surgical, psychiatric and physical methods of treatment are described, with their application in cases of injuries to the central nervous system and in those involving reconstructive and plastic surgery and orthopedics. A book by Davis<sup>7</sup> is a valuable guide to treatment of neuro-psychiatric disorders and is based on the author's

wide experience in the Veterans' Administration Facility. Hudson and Fish's<sup>8</sup> *Occupational Therapy in the Treatment of the Tuberculous Patient* is recommended to physicians interested in this field, although it is primarily written for students of occupational therapy. The more technical aspects of physical therapy, particularly mechanotherapy, are described in detail by Smith<sup>9</sup> in *Rehabilitation, Re-education and Remedial Exercise*. A short manual by various authors entitled *After-Care and Rehabilitation*, edited by Rolleston and Moncrieff,<sup>10</sup> also gives detailed information on physical-medicine procedures. Three new books have appeared, *Physical Medicine in General Practice*, by Bierman,<sup>11</sup> *Technic of Electrotherapy*, by Osborne and Holmquest,<sup>12</sup> and *Manual of Physical Medicine* by Kovacs.<sup>13</sup> Especially recommended are the manuals on physical therapy and occupational therapy available in reprint form through the American Medical Association, which may serve as practical guides to physicians in the armed services.

#### PHYSICAL MEDICINE FOR TRAUMATIC CONDITIONS

In military practice the lesions most frequently benefited by physical medicine are traumatic in origin. Krusen<sup>2</sup> has divided these into two large groups — trauma of bones and joints, including fractures, dislocations, stiff joints, bone grafts and traumatic arthritis, and trauma of soft tissues, including scars (particularly of amputation stumps), contusions and lacerations of muscles and tendons, postural strains (particularly backache and flat-foot), paralysis (especially as a result of peripheral nerve injuries) and tendon transplantations.

Although no striking changes in technic have recently been developed, appreciation of the benefits to be derived from physical therapy in traumatic conditions is not yet widely disseminated throughout the medical profession as a whole. In summarizing the principles of physical medicine as described by Pemberton,<sup>14</sup> it can be stated that the central agencies of physical therapy consist of heat, massage, rest and exercise. Exposure to heat is accompanied by a rise in body temperature, an increase in the heart rate and peripheral vasodilatation. A great increase in rate of circulation occurs throughout the body, with leukocyte diapedesis into neighboring tissue, and hence phagocytosis and other influences on fixed tissues. Total metabolic activity is increased and the lymph flow is accelerated. The use of heat locally and sometimes systemically paves the way for massage.

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About 25 per cent of the blood of the body is in the capillary beds, many of which are near the surface or at the periphery. Stroking of capillary beds induces changes in the caliber of the capillary vessels, an acceleration in the rate of blood flow through them, a rise in the peripheral blood-cell count and a migration of leukocytes. Some cellular and acinous contents of certain organs can be expressed or changed in distribution. There is no production of lactic acid following massage, such as accompanies voluntary use of muscle, or of alkalosis, such as follows exposure to heat. Extravasations of blood or débris into tissue from trauma can be removed by massage more quickly than would otherwise occur. Improper use of massage, may, of course, draw blood away from regions greatly needing it and so lead to fatigue and depletion. Exercise, which affords the only means of developing muscle, has some of the effects on capillary beds produced by heat and massage. So-called "postural exercise," involving deep breathing and achievement and maintenance of better posture in recumbency, goes far to compensate for loss of bodily activity and has great value for persons confined to bed or a sedentary life. Rest is also important in physical therapy. Pemberton also states that there is probably no other field of medicine in which early and full grasp of the principles at stake would have equally significant results in returning soldiers to duty and in reducing invalidism. Some of the ordinary applications of physical therapy in traumatic surgery will be described in more detail.

### *Fractures*

Successful treatment of fractures is not based solely on securing bony union but also on the rapidity with which full working function is obtained. The type of aftercare of fractures may influence considerably the functional result, particularly the speed of recovery.<sup>15</sup> The proper aftercare of a fracture consists of maintenance of fixation until union has occurred, early restoration of efficient circulation, development or preservation of muscular tonus and power and guidance in obtaining normal co-ordinated skillful joint motion. The purposes of physical therapy have been outlined as follows:

Promoting the early absorption of hemorrhage and traumatic exudate; relaxation of muscle spasm to relieve pain and discomfort; re-establishment of normal circulatory conditions in the affected extremity, blood stream and lymphatics, which ensures a more rapid and complete healing of the fracture; and building up in the muscles of the extremity that tone and flexibility so necessary to normal use. These effects are brought about by physical agents acting on the neuromuscular and neurovascular reflex mechanisms and through stimulation of muscles by physical means or voluntary action.<sup>16</sup>

To accomplish these purposes the following physical agents are used: heat, massage, muscular stimulation and occupational therapy. Heat may be applied in the form of radiant-heat lamps, whirl-

pool baths, hot packs or diathermy, preferably of low intensity and sustained duration. Massage consists of light stroking alone in the early stages and deeper stroking later, it being borne in mind that the beneficial effects are obtained more by reflex stimulation than mechanical force. Under muscular stimulation, contractions are obtained preferably by inciting voluntary efforts, either within a guided range of motion or by stationary contractions, such as so-called "setting exercises." In some cases, particularly those in which prolonged immobilization is necessary, electrical stimulation with a tetanizing current (sinusoidal or faradic) is a valuable aid in preventing muscle atrophy and fibrosis and in improving circulation. When a proper degree of firm union is obtained, the patient must be instructed and encouraged in graded active and functional use of the affected parts. Occupational therapy emphasizes the value of functional, properly graded activities as incentives to the development of strength and skill and as a means of overcoming psychologic handicaps to recovery.

### *Sprains and Dislocations*

Cold rather than heat, compression bandages and elevation are recommended for the immediate treatment of sprains. Later the measures described for aftercare of fractures are suitable, with proper grading of exercises an essential feature. When joints have become stiff from traumatic arthritis, chronic bursitis or other cause, too much must not be expected of heat and massage. Return of function is dependent on proper stretching by active and assisted exercises. At times this may be supplemented by splinting and traction.

### *Scar Contractures*

Limitation of motion secondary to contracture of scar tissue after burns or other soft-tissue injuries may require prolonged physical therapy. In case of hand involvement specially designed splints allowing motion have been described.<sup>17, 18</sup> Mild heat in the form of a whirlpool bath or paraffin bath has been recommended, as well as a special type of massage to improve circulation and loosen adhesions, followed by active exercises and graded functional activity as prescribed in occupational therapy.<sup>19</sup>

### *Amputations*

In preparing stumps for early use, heat, massage and exercises are helpful.<sup>20</sup> Moderate radiant heat may be used to stimulate circulation, and also whirlpool baths, with avoidance of excessive use and softening of the skin. Massage also aids in promoting circulation. Of special importance is a program of exercises to develop the strength of the musculature. These are graded to include resistive exercises four times daily. Physical therapists should also instruct patients in the mechanics of using an

artificial limb and walking with walkers, crutches and canes.

### *Peripheral-Nerve Injuries*

Physical therapy in injuries to the peripheral nerves includes the use of proper splinting to prevent overstretching of paralyzed muscles by gravity or antagonistic strong muscles.<sup>21</sup> This should not be constant, since severe joint contractures may thus develop. In cases of paralysis splints should be removed for heat and massage to improve circulation and for passive exercise to prevent joint stiffness. Recent studies have indicated that adequate stimulation with low-frequency interrupted direct or alternating currents is useful in lessening atrophy, preventing fibrosis and hastening return of function with reinnervation.<sup>22, 23</sup> Quantitative electrical tests familiar to the specialist in physical medicine are also of aid in evaluating the extent of neural damage and in following the progress of regeneration.<sup>24, 25</sup>

### *Spinal-Cord Injuries*

The treatment of injuries to the cervical, thoracic and lumbosacral cord has been adequately described in recent reports by Munro.<sup>26, 27</sup> The usual physical therapeutic measures useful in spastic paralysis are employed.<sup>28</sup> The frequent finding of atrophic stiff hands in the cervical injuries was noted by Munro, who suggested that it might be due in part to vitamin deficiency. He recommends giving intensive treatment with vitamin B complex, in addition to early and continuous physical therapy.

### HEALTH RESORTS

British physicians have found that health resorts are invaluable as centers for those disabled in war. In the United States, also, rehabilitation centers have been set up in such localities. The United States Army Medical Corps, for example, has established them at White Sulphur Springs, West Virginia, Colorado Springs and Denver, Colorado, Hot Springs, Arkansas, Battle Creek, Michigan, Swananoa (near Asheville), North Carolina, Tucson, Arizona, and Miami, Florida. The Bureau of Medicine and Surgery of the United States Navy has established hospitals at Asheville, North Carolina, Yosemite, California, Glenwood Springs, Colorado, and Sun Valley, Idaho. The Veterans Administration, it is said, is contemplating the establishment of hospitals at such health resorts as Saratoga Springs, New York, Hot Springs, Utah, Hot Springs, South Dakota, Bay Pines, Florida, and Mineral Springs, Texas.

The exact sphere of usefulness of treatment in a health resort as part of a broad plan of total rehabilitation has been shown by Krusen.<sup>5</sup> He outlines the steps in a complete plan for total rehabilitation as follows: immediate emergency care,

secondary emergency care, care during transportation, general hospital care, care in rehabilitation centers, vocational guidance, vocational training, selective placement and industrial rehabilitation. He states that health resorts will be utilized most frequently as rehabilitation centers, with vocational guidance and vocational training included. In some instances health resorts can fit into general hospital care, the hospital being located at the resort. Selective placement can occasionally be arranged at the health resort before establishing a permanent home in civil life.

In order that American physicians may have more accurate knowledge about spa therapy and its range of usefulness, a series of articles have been published by distinguished specialists in the field under the auspices of the Committee on Health Resorts of the American Medical Association. In these papers are discussed the effects of climate on disease<sup>29, 30</sup> the role of rest, exercise and diet,<sup>31</sup> underwater therapy,<sup>32</sup> the biologic action of trace elements<sup>33</sup> and the nature of natural therapeutic agents, such as mineral waters and peloids.<sup>34</sup> Articles are also devoted to the physical equipment,<sup>35, 36</sup> types of treatment available,<sup>37, 38</sup> administration<sup>39</sup> and economic aspects.<sup>40</sup> The subject of hydrology and spa therapy is in fact deemed so important that plans have been made to establish a research center in physical medicine, with emphasis on acquiring more fundamental knowledge relative to this type of therapy.<sup>41</sup>

### CONVALESCENT RECONDITIONING

An aspect of rehabilitation that is receiving special attention in the armed services is that of planned convalescent care. Thorndike<sup>42</sup> has stated:

The Surgeon General's reconditioning program is divided into four main phases: physical, educational, occupational and recreational. The physical portion of the program is designed to allay the deteriorated factors coincident with recumbency in bed by use of special bed exercises designed to maintain body tone and vigor and, when indicated, is often focused to strengthen a particular portion of the body. As the patient's strength increases and he becomes ambulant, these exercises are gradually increased in tempo and dosage and are supplemented by various types of athletic games and recreational sports. Physical therapy, when indicated, is co-ordinated with this regimen. Occupational therapy is an important part of the treatment of many patients. It is used both as a functional and a diversional type of therapy. Efforts are made to integrate closely the educational activities with the occupational therapy in order to double the effect of each. Co-ordination of occupational therapy with physical therapy is being effected with good results.

Huddleston<sup>43</sup> has reported the effective use of a convalescent ward at the Fitzsimons General Hospital. Drewyer<sup>44</sup> and Lowman<sup>45</sup> have described similar arrangements in the Navy. Special programs have been outlined for psychiatric casualties.<sup>46</sup> The methods in use in the Army Air Forces have been especially efficient.<sup>41</sup>

Civilian hospitals will do well to incorporate applicable portions of these plans for convalescent care, both to ease demand of beds by speedy convalescence and for the welfare of the patient. The need for research in this field is made apparent by a series of papers indicating the ill effects of complete bed rest.<sup>47-52</sup> Hansson<sup>53</sup> has shown how physical therapy may be utilized to counteract the bad effects of rest and to "turn out a discharged patient with adequate circulation, better muscular tone, better posture, a normal functioning gastrointestinal tract, better skin and a mind that is mentally alert instead of depressed."

A closely related subject is that of the physical fitness of so-called "normal" persons. Its importance is indicated from the finding that one out of four of the teen-age registrants fails to pass the Selective Service examination. Studies have been made in determining methods to evaluate physical fitness and to quantitate the effects of training.<sup>54</sup> Already plans have been made to establish a national program for physical fitness.<sup>55</sup>

### INDUSTRIAL REHABILITATION

Industrial concerns and insurance companies are beginning to realize the importance of medical care that goes beyond hospital medicine and surgery and includes convalescent care and industrial rehabilitation. Howitt<sup>56</sup> has described a center in England constructed on the lines adopted for army practice. Aitken,<sup>57</sup> Coulter,<sup>58</sup> Zeiter<sup>59</sup> and others<sup>60, 61</sup> have reported similar setups established in this country. Both physical and occupational therapy are extensively employed, particularly in the early stages after injury. Activities are later directed toward vocational guidance and placement in jobs appropriate for the degree of handicap. The program of the Caterpillar Tractor Company, including job analysis and the use of 800 handicapped employees, is an outstanding example of success in rehabilitation.<sup>62</sup>

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The wide scope of physical rehabilitation and its importance in wartime are now apparent. One of the most serious needs is trained personnel for convalescent centers. Teachers are also needed to instruct a new group of specialists in this field. Already teaching and research centers in physical medicine have been established for this purpose in a number of leading university medical centers. The old term "physical therapy" has now been largely replaced and a new specialty, "physical medicine," is being established. A comprehensive and enlarged view of physical medicine in rehabilitation can be gained from the following quotation:

It seems that there are two definite phases: first, physical medicine as it pertains to definitive treatment and how it can be utilized by the physician in the diagnosis and treatment of disease; secondly, — and which I think is the more or less new concept as far as the general medical profession is concerned, — its utilization in the broad field, taking up the dead space between definitive care and ability

to return to productive work, the setup for retraining and reconditioning, medicine and its relation to environment, occupation, social status and so forth. It is going to take physicians with real training and background to meet this special need; it should be the broadest of all medical specialties, utilizing as a basis for physical medicine the great potentialities of oneself. This would be more or less the science of how to use these potentialities and the art of such application.<sup>63</sup>

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor\**

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### CASE 31071

#### PRESENTATION OF CASE

A four-and-a-half-month-old infant was admitted to the hospital because of opisthotonos and failure to gain weight.

The infant was born six weeks prematurely after a normal labor of five and a half hours. The pregnancy was complicated by toxemic symptoms. The birth weight was 5½ pounds. After three and a half weeks in an incubator the child was discharged home, but was a poor feeder and gained weight very slowly, the weight on admission to this hospital being only 8¼ pounds. The mother noted that the child cried a great deal and often turned blue after a crying spell. The child also tended to lie in an opisthotonic position, with the back arched and the head held well back, especially when crying. He could support his head. There was no history of jaundice or convulsions. On several occasions the child had had a running nose but had never been febrile.

Physical examination revealed a spastic, irritable child, often opisthotonic and crying almost constantly; there was a click-clack sound to the breathing after the crying ceased. There was slight cyanosis of the face, especially about the mouth and most marked during crying spells. The skin was clear. The muscles appeared unusually well developed. The head was malformed, with a definite bulge over the

occipital region. There was considerable exophthalmos, estimated at about 4 mm. The pupils reacted normally, and the fundi were negative. The ears were negative. There was questionable enlargement of the lateral lobes of the thyroid gland, and a thrill and bruit were noted over this area; the bruit could also be heard in the lower temporal regions. The lungs were clear. Examination of the heart revealed the point of maximum impulse to lie just below and beyond the nipple line. The rate was rapid and regular. A systolic murmur was heard all over the precordium, loudest in the fourth and fifth intercostal spaces, just lateral to the left sternal border; it was transmitted to the neck and back, shifting somewhat with change in position. The pulmonic second sound was greater than the aortic, but both were prominent. The liver was felt three fingerbreadths below the costal margin, and the spleen was palpable. All the extremities were spastic, the legs more so than the arms. The deep tendon reflexes, especially those of the lower extremities, were exaggerated. The Babinski, Oppenheim and Gordon signs were positive bilaterally. The abdominal reflexes were absent, but other superficial reflexes were normal.

The temperature was 100°F, the pulse 145, and the respirations 45. The blood pressure was 146 systolic, 40 diastolic.

Examination of the blood on admission revealed a red-cell count of 4,500,000, with 90 per cent hemoglobin, but subsequent counts averaged about 3,500,000, with 70 per cent hemoglobin. The white-cell count was 14,000, with 59 per cent neutrophils, 27 per cent lymphocytes, 7 per cent monocytes, 1 per cent eosinophils, 1 per cent basophils and 3 per cent myelocytes. The red cells and platelets appeared normal on smear. The urine was negative. The bleeding and clotting times were both within normal limits. The serum nonprotein nitrogen was 30 mg. per 100 cc., the protein 6.4 gm., the calcium 9.8 mg., the phosphorus 6.1 mg. and the alkaline phosphatase 3.9 Bodansky units. The sodium was 136.1 milliequiv. per liter, the potassium 5.6 milliequiv., and

\*On leave of absence



the chloride 98 milliequiv. The van den Bergh reaction and the prothrombin time were normal. Nose and throat cultures were negative, as were cultures of the blood, spinal fluid and stools. A blood Hinton test, including dilutions, was negative. Determinations of the serum protein-bound iodine on the third and fourth hospital days were 9 and 9.3 microgm. per 100 cc., respectively (these are borderline, high-normal values).

A roentgenogram of the chest revealed marked enlargement of the heart to the left but no definite evidence of transposition of the vessels or engorgement of the pulmonary artery. The lungs were clear. Roentgenographic examination of the skull revealed bones of normal texture and density. The posterior fontanelle was closed, and the anterior fontanelle open, and there was no separation of the sutures. Lateral examination of the neck revealed widening of the posterior pharyngeal wall without tracheal obstruction. The thoracolumbar spine and bones of the lower legs were normal.

A lumbar puncture on admission yielded clear fluid dripping out slowly and containing 70 fresh (uncrenated) red cells and 1 to 2 lymphocytes per cubic millimeter. The Wassermann test was negative, and the sugar and protein were normal.

The patient's temperature ranged between 100 and 103°F. for the first four days, thereafter remaining approximately normal except for a brief rise to 103°F. on the seventh hospital day. The pulse continued to range between 120 and 180, and the respirations between 35 and 80. The blood pressure varied considerably, with high systolic and low diastolic pressures; one observer reported a reading of 300 systolic, 0 diastolic, on one occasion.

The child was given 2 cc. of paraldehyde in oil every four hours for sedation, 8 mg. of sodium phenobarbital being substituted after a few days. A diarrhea with three to six loose stools daily developed on the third hospital day and continued thereafter. Six thousand units of penicillin was administered every three hours over a period of nine days, and because of the diarrhea and poor appetite, the child was maintained for short periods on parenteral fluids. On the fifth hospital day thiouracil therapy was begun, 25 mg. being administered every six hours, and on the seventh day 2 drops of saturated potassium iodide solution was instituted daily as well. Although some observers thought that the size of the thyroid gland was diminishing, irritability, hypertonicity and frequent opisthotonic spasm continued.

On the twenty-first hospital day the child suddenly went into collapse, with gasping respirations and cyanosis. The pulse fell to 88, and the blood pressure to 78 systolic, 50 diastolic, and he seemed more relaxed than previously. A lumbar puncture at that time revealed fluid containing 500 fresh red cells but no white cells per cubic millimeter, 3 cc. of fluid being removed only with great difficulty. Ven-

tricular taps on the following day revealed slightly bloody fluid containing 3800 fresh red cells per cubic millimeter on the left and cloudy fluid containing 800 fresh red cells on the right. The Pandy test was negative, and the sugar normal.

The child was treated with oxygen, 10 cc. of adrenocortical extract and glucose intravenously. During the ensuing thirty hours the child had frequent attacks of breathlessness and cyanosis and the pulse fell to 40 in spite of various stimulants. Death occurred on the twenty-third hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. ROBERT WILLIAMS\*: The nature and number of the observations made in this case are such that in the search for their solution one is led through most of the main general divisions of pathology. It is necessary to give some consideration to traumatic birth injuries, infections, neoplasms, metabolic disorders and congenital anomalies. The accumulated data in the case are such as to make one consider direct or indirect involvement of widespread sites in the body. There are suggestions of disorders in the head, neck, chest and abdomen. At the outset, however, it should be mentioned that in children, particularly in infants, one may observe symptoms and signs in several systems other than the ones directly involved. For example you will recall how commonly one sees evidence of central-nervous-system stimulation and gastrointestinal-tract alterations in a large number of diseases of childhood that cause no direct involvement of these systems. It is also well to recall that, for a given amount of disease, children respond much more markedly with changes in temperature, pulse rate, blood pressure and respiratory rate. Moreover, in some respects the physical signs in normal, as well as in abnormal children, differ from those of adults. For example, the liver edge is more frequently palpated in normal children. The tendon reflexes are often exaggerated, the abdominals absent, and the Babinski positive. In infants there may be serious cardiac lesions producing a paucity of physical signs, whereas in adults the same type of lesion usually causes pronounced signs. Finally, a young child is not likely to have multiple diseases, although there may be multiple disturbances of the same general nature.

With these general principles in mind we may next consider critically the data presented chiefly in the light of anatomic disturbances and without an attempt to integrate the entire picture. Alterations in the nervous system should be considered seriously because of the marked irritability, the hypertonicity, the opisthotonos, the bulging in the occipital region, the hyperactive reflexes, the positive Babinski, Gordon and Oppenheimer signs and the bloody cerebrospinal fluid. The frequent insignificance of many of these signs, however, has

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already been discussed. It can also be pointed out that there is a condition, designated as the hypertonic infant, in which no significant pathologic alteration has, to my knowledge, been found, with some of the characteristics of the case under consideration: irritability, prolonged crying, hyperactive tendon reflexes, muscle spasm, opisthotonos, flexion of the arms and legs, clenching of the hands, diarrhea and a slow gain in weight. It is to be emphasized that although the cerebrospinal fluid was bloody on four occasions, each time the red cells appeared fresh, and there was no xanthochromia, increased protein or increased white-cell count. Furthermore, there was no evidence of increased spinal-fluid pressure. Therefore, although the central-nervous-system changes are suggestive of disease, they are not convincing.

Exophthalmos is often a helpful sign, but it may occasionally be misleading. In addition to being a manifestation of Graves's disease, it may be due to tumors or infections in the orbit, increased venous pressure, small orbits and retention of orbital fluid, as in nephritis and hypertension. It may also be a racial characteristic, occurring especially in Italians. The equality of the exophthalmos on the two sides, the absence of obvious edema of the orbits, the absence of papilledema, and the absence of evidence of abnormal masses in the cranium help to reduce the etiologic factors that must be considered.

In considering the bruit in the neck it must be stressed that, whereas it was heard over the thyroid gland, it was also heard at the base of the skull. Whether the bruit was of the same order as the murmur heard in the neck and back and over the precordium must be borne in mind. It is of significance that no masses or dilated vessels were palpated in the neck or elsewhere. The thyroid gland was questionably enlarged, but whether the enlargement was due to Graves's disease, to increased vascularity of the neck or to some other cause must be considered.

The changes in the cardiovascular system are the most convincing of any. There is no reasonable doubt about the heart being distinctly enlarged. The repeated blood-pressure estimations revealed a distinct elevation in the systolic pressure and a drop in the diastolic pressure. The murmur heard over the lower precordial region, back and neck was of sufficient intensity to appear significant. The pronounced tachycardia, tachypnea and some cyanosis indicate that the cardiovascular system was burdened.

The liver may be considered to have been slightly enlarged, as perhaps the spleen.

Aside from the roentgenograms the laboratory findings are of no particular aid, except by their negative character.

In the differential diagnosis I have given some consideration to a rather large number of diverse conditions, among them being brain tumor, various

infections, traumatic injuries, Graves's disease, von Gierke's disease, the infantile type of Gaucher's disease, Niemann-Pick's disease, pheochromocytoma, venous hums, arteriovenous aneurysm, patent ductus arteriosus, coarctation of the aorta, patent septal defects and a number of other congenital heart diseases. To be sure, I readily dismissed many of these entities from consideration since, although they satisfied some criteria, they were at a loss in explaining others. Since most of the positive data had reference to the cardiovascular system, and since this was an infant who apparently had never been well, chief consideration was given to congenital cardiovascular anomalies. The chief problem is to explain a large heart with presumably competent valves but with peripheral manifestations of aortic insufficiency and with murmurs or bruits over the lower precordium, back, neck and temporal regions. Lest I have been too hasty in discarding some of the data, however, I shall briefly review the features of this case in the light of other diseases.

Let us consider brain tumor. There were no convincing neurologic signs of a brain tumor and no definite abnormalities of the cerebrospinal fluid—at least the abnormalities present are open to question. There was a negative skull plate. There were many positive cardiovascular signs, indicating that there was a great deal of trouble other than what might have been caused by a brain tumor.

Infection is suggested by the fever, the tachycardia and so forth; but against infection are the negative cultures from many sites. Infection could not explain many of the cardiovascular findings, but it still might be considered as the cause of the terminal event.

The next condition to discuss is trauma. This is considered particularly because of its etiologic significance in arteriovenous aneurysms. There was no history of injury at birth or subsequently, and there was no definite physical evidence of it.

Metabolic disorders might be discussed next. The first among these is thyrotoxicosis. As a matter of fact, as one rapidly reads the characteristics of this infant's disease there are many features that one might consider as favoring thyrotoxicosis. For example, the four cardinal features of thyrotoxicosis in children are readily apparent: exophthalmos, nervousness, questionable goiter and tachycardia. Against this diagnosis, however, are the extreme rarity of the disease at this age, the essentially normal protein-bound iodine and the fact that the response to treatment was not particularly good. Furthermore, thyrotoxicosis will by no means explain all the cardiovascular features.

The next condition for consideration is von Gierke's or glycogen-storage disease. In favor of it is the extremely large heart with some enlargement of the liver and perhaps splenomegaly. It is also of some little interest in this connection that the child

was said to have been well developed muscularly; in this disease one may actually get hypertrophy of some of the muscles. Von Gierke's disease, however, does not explain the wide pulse pressure or the murmur.

This child had certain features that one observes commonly with Gaucher's disease, although they are not pathognomonic of the disease, these being the rapid course of the disease, the nervous symptoms, the slow weight gain, the enlarged liver and spleen, the opisthotonos, the increased reflexes and the spasticity of the limbs. But I find it difficult to explain the cardiovascular findings on this basis.

Some of the comments that I have made on Gaucher's disease apply to Niemann-Pick's disease and Schüller-Christian's disease. The latter need not be given much consideration. It might explain the exophthalmos, but there was no defect in the bones, and no diabetes insipidus, and this disease would not explain the cardiovascular changes.

Finally we come to the congenital anomalies. As I have mentioned before, the fact that the child's trouble dated from birth and the fact that most of the features seemed to be related to the cardiovascular system make one begin to give great emphasis to the possibility that there was a congenital anomaly somewhere in the vascular system.

First we might consider the possibility of a cranial arteriovenous aneurysm. Although I have cast some doubt about the validity of the neurologic data, both clinical and laboratory, and whereas there is good reason for attributing significance to certain specific observations when one considers them as a whole, they do indicate that there might have been organic disease somewhere in the cranium. Arteriovenous aneurysm in the cranium would explain the bruit that was heard at the base of the brain. Such a bruit is one of the most characteristic features of such a lesion. It might also explain the exophthalmos. To be sure, when there is exophthalmos on the basis of arteriovenous trouble it is apt to be unilateral, but I can conceive how it could be bilateral. Furthermore, one can consider the peripheral vascular manifestations, simulating aortic insufficiency, as being on the basis of arteriovenous aneurysm, but I must say that the peripheral changes are quite pronounced and out of proportion to what one usually observes with such an abnormality.

We might consider a cervical arteriovenous aneurysm or one in the extremities. Such an entity would account for the high pulse pressure, with a high systolic and a low diastolic pressure, cardiac dilatation and hypertrophy, cyanosis, tachycardia and the bruit in the neck. Furthermore, in peripheral arteriovenous aneurysm, murmurs in the heart have been described, even though there is no direct abnormality in the heart itself, although, to be sure, these murmurs are usually not very loud. Against the possibility of arteriovenous aneurysm

in these sites is the fact that we have no mention of evidence of localized venous engorgement or edema. I believe that, with all the peripheral alterations in the vascular system, one should be able, particularly in a small child, to palpate the arteriovenous mass, unless it was hidden in the brain or in the thorax.

We may consider a patent ductus, which is also an arteriovenous aneurysm but is located in the chest. In favor of this are the signs of an arteriovenous aneurysm in the absence of a peripheral arteriovenous aneurysm. There are loud pulmonic and aortic second sounds, with the pulmonic being louder than the aortic. With patent ductus arteriosus the most classic feature is a machinery-like murmur, which one hears almost always in the second left interspace, close to the sternum. That murmur is absent here. The second most important point, a characteristic configuration of the heart and great vessels, was not present in this case.

Coarctation of the aorta should be considered because of the high systolic pressure that was found in a child that had a good chance to have a vascular anomaly. The diastolic pressure, however, was definitely low, and unless there was some other abnormality associated with coarctation, the diastolic pressure should have been normal, if not elevated. There were no murmurs or other good physical signs indicating the presence of the stenosis. Because of the relatively loud murmur heard in the fourth and fifth interspaces parasternally on the left, and because of the absence of good evidence for valvular disease and murmurs in the region of the base of the heart, one should probably also consider the possibility of interventricular septal defect. This child could well have had this abnormality. There is not much evidence for it, but it is difficult to rule it out.

In conclusion, on considering the picture as a whole, it seems to me that the data indicate that this child had an arteriovenous shunt, accompanied by cardiac dilatation and hypertrophy. The evidence available does not permit one to say specifically where the shunt was located. The best I can say is that it was either in the cranium or in the thorax.

DR. NATHAN B. TALBOT: I saw this child during the early part of the hospital stay and am frank to admit that clinically, with the aid of numerous consultants, it was impossible to come to any definite conclusion. Although we carefully considered the possibility that the infant had thyrotoxicosis, we also were at times worried that there was a significant intracranial lesion of some type.

DR. CLEMENS E. BENDA: I think that the neurologic symptoms did not attract sufficient attention. Even if the positive Babinski sign was of little significance, the child had opisthotonos and severe spasticity. There was flexion of the legs and of the arms, with clenched fists. The head was bent back-

ward, and the eyes showed protrusion, which is so frequently seen in infants with intracranial hemorrhage, as demonstrated by Dr. Ingraham.\*

I do not see how anyone can explain the neurologic symptoms on the basis of anything except an intracranial lesion, and I do not believe that one can disregard the possibility of an intracranial hemorrhage. Although prematurity in itself is of no pathological significance, many studies have

dependent of hyperthyroidism. The child had definite exophthalmos, particularly marked in the side view, and a loud bruit in the neck; he was extremely active and underweight. I believe that I was alone in thinking that the thyroid gland was enlarged—I was quite sure that both lobes were increased in size. The child seemed to possess all the criteria necessary to make a diagnosis of Graves's disease. When the blood iodine came back as 9

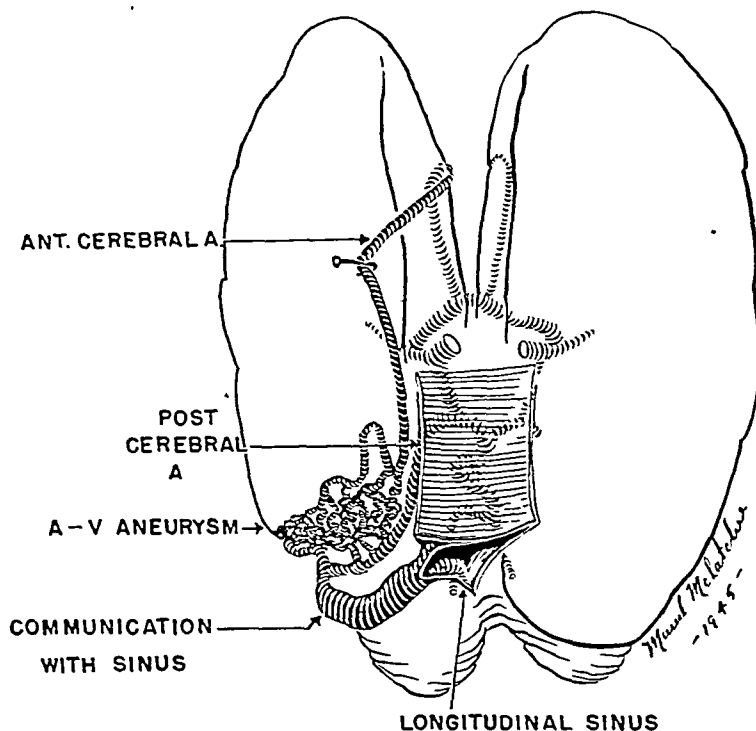


FIGURE 1.

demonstrated that premature babies are particularly likely to have intracranial hemorrhages because of the immaturity of their vascular system. The frequency of intracranial hemorrhages increases with the decrease in birth weight. For example, 76 per cent of all premature babies weighing less than 3½ pounds were found to have some kind of intracranial hemorrhage. Since this child did not have immediate dramatic symptoms after birth it is probable that the lesion was related to the venous system, from which blood was seeping out slowly, the difficulty not becoming recognizable until several weeks after birth.

DR. JACOB LERMAN: When I saw the youngster I thought that the most important diagnosis to be considered was hyperthyroidism, with or without an accompanying neurologic disorder. In other words, the neurologic picture seemed to be in-

dependent of hyperthyroidism. The child had definite exophthalmos, particularly marked in the side view, and a loud bruit in the neck; he was extremely active and underweight. I believe that I was alone in thinking that the thyroid gland was enlarged—I was quite sure that both lobes were increased in size. The child seemed to possess all the criteria necessary to make a diagnosis of Graves's disease. When the blood iodine came back as 9

microgm. per 100 cc., which is a high normal, it seemed to be confirmatory of the diagnosis. It is true that in the end the patient did not do well, but in the first few days he seemed to improve and, as I recall, the impression of hyperthyroidism became more plausible. Such a diagnosis, however, did not explain his other manifestations.

DR. TALBOT: I can back up Dr. Lerman's remarks by the statement that this baby presented the most extraordinary degree of hyperactivity, seemingly not only physical but also, one might say, metabolic.

#### CLINICAL DIAGNOSIS

Thyrotoxicosis.

#### DR. WILLIAMS'S DIAGNOSES

Arteriovenous aneurysm, cranial or thoracic.  
Cardiac dilatation and hypertrophy.  
Terminal infection.

\*Ingraham, F. D., and Matson, D. D. Subdural hematoma in infancy. *J. Pediatr.* 24:1-37, 1944.

## ANATOMICAL DIAGNOSES

Cerebral arteriovenous aneurysm.  
 Cardiac hypertrophy and dilatation.  
 Bronchopneumonia.  
 Pulmonary edema.

## PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy on this child showed a thyroid gland that weighed 1.4 gm. and, so far as we could tell, showed no evidence of hyperplasia or hyperactivity, such as one would see in hyperthyroidism. The heart was more than normal in size, weighing 55 gm., the normal weight of the heart in a child of this age being about 20 gm. There was hypertrophy of the left ventricle, but no anomalies. The child had a terminal bronchopneumonia, a bit suggestive of the aspirative type; the bronchi were filled with purulent exudate, as were the surrounding alveoli. There was also a rather severe pulmonary edema. The real disease was in the cranium, however, and I shall ask Dr. Kubik to describe it.

DR. CHARLES S. KUBIK: I should like to congratulate Dr. Williams on his excellent discussion.

The left occipital lobe was absent—whether through degeneration or lack of development is not altogether clear. At the posterior extremity of the defective left cerebral hemisphere there was a cluster of thin-walled, tortuous blood vessels that communicated through a large venous channel with the superior longitudinal sinus and, through arterial branches, with the left anterior cerebral and left posterior cerebral arteries. All the arteries supplying the arteriovenous aneurysm with blood were enlarged to at least three or four times the size of the corresponding normal arteries—as is the rule with any artery proximal to an arteriovenous fistula. The arteries affected were both vertebrals, the basilar, both internal carotids, the left anterior cerebral, the left posterior cerebral and the right anterior cerebral only as far as the anterior communicating artery (Fig. 1). Cardiac enlargement is also found in these cases.

Two patients with similar arteriovenous aneurysms, having connections between the anterior and posterior cerebral arteries and the superior longitudinal sinus, have come to autopsy at this hospital. One was a man in his early twenties, and the other was a man about sixty years old. The former died as the result of hemorrhage from the abnormal vessels. The other had a subdural hematoma. In both cases, calcification of the abnormal tortuous vessels was visible by x-ray. In still another case the patient was a woman of twenty-eight with multiple arterial connections between a greatly enlarged lateral sinus and the basilar, middle meningeal and occipital arteries.

Thus patients with intracranial arteriovenous aneurysms may live many years, and I should not

suppose that death in the present case was caused by the arteriovenous aneurysm. A possible explanation of exophthalmos was increased venous pressure transmitted from the superior longitudinal sinus through anastomotic veins to the cavernous sinuses and from there to the ophthalmic veins.

## CASE 31072

## PRESENTATION OF CASE

A sixty-four-year-old married multiparous woman was admitted to the hospital with pain in the right lower quadrant of the abdomen.

About one year prior to admission the patient noted an intermittent dull aching pain in the abdomen, at first centered about the umbilicus but soon localizing in the right lower quadrant. It was associated with some tenderness and accompanied by nausea. There was no vomiting, diarrhea, fever or chills. This pain lasted about six days, after which all symptoms disappeared. During the following year she had two or three similar episodes, each lasting about a week. During some of them she was bedridden. She kept about her housework but complained to her family of "soreness in the right side." Seven weeks prior to admission she noted a recurrence of the distress, at first intense about the umbilical area and finally localizing as "soreness" in the right lower quadrant. This attack lasted until the time of admission. She was nauseated mildly on two occasions, never vomited and experienced no chills or fever. She had tended to be constipated for years, and there had been no change in this habit. She took laxatives sporadically. She had never noticed any blood.

Ten years prior to admission she had had a hemorrhoidectomy. One of her sisters had died of tuberculosis.

Physical examination revealed a well-developed and well-nourished woman in no acute distress. The lungs were clear. The heart revealed questionable enlargement to percussion. Systolic murmurs were heard at the apex and over the aortic area, and systolic and diastolic murmurs at about the level of the third interspace to the left of the sternum. There was slight tenderness over a definite mass on deep palpation in the right lower quadrant.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 80 diastolic.

The hemoglobin was 13.6 gm. The urine—a voided specimen—had a specific gravity of 1.023, with a + test for albumin and many white cells in the sediment. A stool examination was guaiac negative. A blood Hinton test was negative.

A roentgenogram of the chest revealed increased pulmonary markings throughout. The heart was enlarged, principally in the region of the left ven-

tricle. The aorta was somewhat dilated, and a double ring of calcium was visible at the arch. An intravenous pyelogram revealed some lateral displacement of the right kidney, but no other abnormalities were observed. A round shadow was visible in the right upper quadrant, consistent with a gallstone. The lumbar spine showed mild degenerative changes, all the bone appearing decalcified. A barium enema revealed a retrocecal appendix and an irregular defect lying along the posterior aspect of the cecum and ascending colon corresponding to the palpable mass. The colon was somewhat fixed at that point, but the mucosal pattern appeared to be intact.

On the fifth hospital day a laparotomy was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. LELAND S. MCKITTRICK: I should like to look at the x-ray films, although, as I have said many times, I am never sure whether Dr. Holmes is going to help or disturb me by showing them.

DR. GEORGE W. HOLMES: You should have been here a short while ago when I was discussing the differential diagnosis of a case and had my first opportunity of making the same statement to the surgeons.

The first thing I notice is that in this intravenous pyelogram there is evidence that the patient did not concentrate urine well. The kidneys are about normal in size, and I do not see any definite evidence of tumor. In the chest film I observe a ring of calcification in the aorta and a great deal of arteriosclerosis, with some tortuosity of the aorta and enlargement of the left side of the heart. This picture can go with hypertensive and arteriosclerotic heart disease. It looks to me as if the colon emptied well; they apparently became interested in the cecal area, but I do not believe that they saw anything.

DR. MCKITTRICK: Where is the appendix?

DR. HOLMES: It is retrocecal — an unusual position. There is a tendency for the cecum to contract, possibly because it was somewhat irritated. The cecum is a little high.

DR. MCKITTRICK: As one reads this history it seems too simple. It just cannot be true. I place a great deal of stress on the history in certain conditions. The problem here is, Did this woman have a tumor of the cecum or an inflammatory lesion? If she had a tumor of the cecum, was it carcinoma or lymphoma? If it was inflammatory, was it tuberculosis, a granulomatous tumor such as one gets in regional enteritis or just appendicitis? I do not believe that the patient had carcinoma. Carcinoma gives symptoms that primarily fall roughly into three groups — symptoms because of the anemia that is frequently associated with it, those referable to obstruction and those due to the local inflammatory reaction when the serosal layers are involved. I do not believe that she had a carcinoma a year ago giving symptoms and signs resembling an in-

flammatory lesion in the right lower quadrant with localized tenderness. That, in addition to the absence of evidence of obstructive symptoms, the absence of bowel irregularity and the normal hemoglobin, makes me entirely satisfied to leave carcinoma out of the picture.

I do not know how to bring lymphoma into the picture, or how to rule it out, except that she had no evidence of interference with the mucosal outline. There is nothing one can make out from the x-ray to suggest tumor of the cecum itself, and again the history does not fit into it.

I cannot say that she did not have tuberculosis, however. She had increased lung markings and had had a sister who had died of the disease — in fact, the history does all it can to call our attention to it; but I do not believe she had it.

Here is a woman who had a series of attacks of pain and was well between the attacks, when all the symptoms disappeared. She then had abdominal discomfort localized in the right lower quadrant. Of course that is the picture that we teach students is characteristic of appendicitis. As I read the story and got down to the last attack of several weeks' duration I fully expected to hear about a mass in the right lower quadrant. It apparently was there. Whether or not that was a red herring, I do not know. Chronologically it fitted all right. I thought she had an inflammatory process. If she had an inflammatory process about the best bet is appendicitis. The little appendix stub that Dr. Holmes pointed out fits into the picture perfectly.

She may have had a diverticulum of the cecum with recurrent episodes of discomfort. Although she may have had recurrent episodes of appendicitis during the year before entry, the final attack may have been due to a new disease unassociated with it. But it seems to me that I have to connect up the history of the past year with the story of the findings of this brief admission, particularly when they dovetail into each other all right. I had hoped to be able to give a better differential diagnosis of inflammatory lesions occurring in the right lower quadrant, but to me the only logical diagnosis I can make is appendicitis with an inflammatory reaction — a low-grade appendiceal abscess that we all too frequently see.

DR. JACOB LERMAN: This patient apparently had some form of heart disease, and from the description one has to suspect syphilitic heart disease with aortic regurgitation. She had both diastolic and systolic murmurs with left ventricular enlargement and a normal blood pressure; it could hardly have been due to hypertension so it must have been caused by aortic regurgitation. I should think one would have to tie that in some way.

DR. MCKITTRICK: As I looked at the x-ray films I wondered if it could possibly have been an aneurysm. She had calcification in the aortic knob. She

had, as you say, cardiovascular disease, and I wondered how an aneurysm would fit into the picture. In the first place I do not believe that the history fits it, at least not to my satisfaction. There is no vessel under the cecum that could cause an aneurysm or could cause a mass.

DR. EDWARD HAMLIN, JR.: I should like to hear further discussion of the filling by barium in a chronically or recurrently infected appendix.

DR. MCKITTRICK: I cannot discuss it, but as I looked at the x-ray films, the thin line of barium suggested a nubbin of appendix. How do I know that several centimeters have not sloughed off? When Dr. Holmes showed the film I was not disturbed about it because I thought that fitted into the picture all right.

DR. HOLMES: As a rule, in an appendiceal abscess one does not see the appendix at all, but there are exceptions; I more or less agree with what you say.

DR. ARTHUR W. ALLEN: The man who saw this woman during her attack a year before entry made a diagnosis of appendicitis. Since she was not a good operative risk, he did not take the appendix out at that time. She recovered from that attack down in the country and then had another; since she finally developed a mass that did not go away, he sent her in here.

We also thought that it was appendicitis. So did the X-ray Department. But when we went back over the various cases of appendicitis forming abscess in this region that we had mistaken for tumor, we did not find any with recurrent attacks. All these patients came in with the first episode, when they developed an abscess. We thought that this was inflammatory, since the mass was a little more tender than one would expect with a carcinoma.

We explored the patient under the diagnosis of appendicitis, in spite of the fact that she had had several attacks. When we exposed the area, we could see the whole appendix lying along the lateral wall of the cecum, and palpating through the cecal wall, we easily felt a mushroom-like mass that was about 3 cm. in diameter. We did not disturb it

too much but did an ileotransverse colostomy. Two weeks later we re-explored; the mass had not changed the slightest bit in the interval, which one would expect if it had been an ordinary inflammatory appendicitis. So rather than break into it we took out the right colon. I fear that I spoiled the specimen somewhat, because I wanted to see what it was myself. After taking out the whole mass intact, I eased the appendix off the adherent portion of the cecum. There was a granular area in the wall of the bowel about 2.5 cm. in diameter, but I still did not know the true nature of the process. I thought, however, that it was benign.

#### CLINICAL DIAGNOSIS

Chronic appendicitis, with abscess formation.

#### DR. MCKITTRICK'S DIAGNOSIS

Appendicitis, with chronic abscess.

#### ANATOMICAL DIAGNOSIS

Mucocele of appendix.

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: As Dr. Allen implied, when we received the specimen we had a hard time putting the appendix back where it belonged. The proximal 5 cm. of the appendix looked perfectly normal. The serosa was shiny and thin, not at all edematous; but the tip was gone, and in its place we found some fat and inflammatory tissue that apparently belonged on the wall of the cecum, to which it was adherent. Sections showed a great deal of inflammation surrounding large masses of mucus. I believe that the patient had a mucocele of the distal portion of the appendix that apparently had broken but walled itself off. Since it was a retrocecal appendix, it lay against the wall of the cecum and remained there. There was no evidence of carcinoma. Only the distal 2 cm. of the appendix was involved; this is unlike the ordinary mucocele, which begins at the base and produces a balloon-like enlargement of the appendix.

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## MEDICAL PREPAYMENT-INSURANCE PLANS

AN ITEM published elsewhere in this issue of the *Journal* calls attention to some of the results of a recent survey conducted by the Michigan Health Council, which is composed of the Michigan State Medical Society, the Michigan Hospital Association, the Michigan Medical Service and the Michigan Hospital Service. The survey utilized standard scientific sampling methods to obtain an accurate reflection of public opinion regarding medical matters. The item emphasizes the facts that the people of Michigan have faith in the medical profession, that the majority take advantage of medical-hospital prepayment-insurance plans if they are

available and that medical plans sponsored by physicians are preferable to those offered by insurance companies or to those that might be controlled by governmental agencies.

What applies to Michigan probably represents the attitude of the people of Massachusetts, since the distribution of the inhabitants of the two states according to population density, occupation and income is quite similar. But this must be qualified by the assumptions that the medical prepayment-insurance plan is backed by *all* members of the medical profession, that minor complaints are handled through existing facilities for their adjustment and that the people of Massachusetts are informed concerning the advantages of the Blue Shield.

Many physicians in Massachusetts, particularly specialists, have failed to register as participating physicians with the Blue Shield. A certain number of these object to this inevitable change in the practice of medicine. On the other hand, there are undoubtedly many who refuse because of purely selfish reasons, saying that they "cannot afford to be listed." It is acknowledged that the original fee schedule contained many inconsistencies, which are now in the process of being corrected by groups of specialists, but on the whole, the set fees are reasonable and proper returns for the care of patients whose incomes are sufficiently low to permit them to participate as unlimited subscribers. This opposition on the part of physicians was also experienced in Michigan during the first few years of its medical prepayment-insurance plan, but recently the scheme has received enthusiastic support by the entire profession. Indeed, at the last meeting of the House of Delegates of the Michigan State Medical Society it was unanimously voted that the officers and directors of Michigan Medical Service be commended for their achievement in furnishing several hundred thousand people with medical care on a prepaid basis in a manner that was highly satisfactory to both the patient and the physician and that had resulted in better feeling and understanding between the public and the medical profession.

Another practice that tends to lower confidence is the publicizing of complaints by either subscribers or participating physicians. No plan of



this sort is perfect, particularly in the early days of its existence, but ample facilities have been provided, both in the district societies and in the central organization, for the consideration and ironing out of the difficulties that are sure to arise.

Obviously, a public that is ignorant of the existence of the Blue Shield or of any other medical prepayment-insurance plan cannot be expected to support it. One significant point brought out by the survey of the Michigan Health Council is that three quarters of the people interviewed had never heard of Michigan Medical Service, in spite of the fact that the state has a larger percentage of its inhabitants enrolled in medical-hospital prepayment-insurance plans than has any other state. Such information, of course, must be supplied in Massachusetts either by physicians or by the representatives of the Blue Shield.

The answer to proposals for government-controlled medicine lies in the ability of states or their subdivisions to devise and to consummate plans that aim to correct the deficiencies that are known to exist. The Blue Shield was created by the Massachusetts Medical Society for this very purpose, and all members of the Society should do their utmost to ensure its success.

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## VITAMINS AND GRAY HAIR

IN THE field of vitamins there has sometimes been a tendency in this country for clinical exploitation of the results of laboratory investigations before those findings have been adequately substantiated, and long before their full import and applicability have been ascertained. This has been particularly true in the treatment of conditions in which the evaluation of the results is partly or wholly subjective. One recent outstanding example has been the widely publicized use first of para-aminobenzoic acid and then of pantothenic acid, either alone or in combination with para-aminobenzoic acid, for the restoration of the original dark color of graying hair in man.

Perhaps the earliest experimental production of achromotrichia was by Oettel,<sup>1</sup> who in the course of studies on the toxicity of hydroquinone observed the graying of the fur of cats. Martin and Ans-

bacher<sup>2</sup> several years later confirmed these observations and succeeded in producing achromotrichia in mice that could be cured by the feeding of rice-polish concentrate or of small amounts of para-aminobenzoic acid. They believed that the latter was a factor in the vitamin B complex. Ansbacher<sup>3</sup> also claimed that para-aminobenzoic acid was a vitamin essential for the growth of chicks and that it was also required by rats for growth and for the maintenance of normal fur. In the rat it has since been shown that a deficiency of pantothenic acid causes poor growth, dermatitis, adrenal hemorrhages and graying hair.<sup>4</sup> There is reason to believe, however, that achromotrichia is probably a multiple deficiency of para-aminobenzoic acid, pantothenic acid and inositol and that there are certain interrelations between these substances and perhaps others as well.

In the course of studies on the action of sulfonamides, Woods<sup>5</sup> showed that certain yeast extracts contained a substance that prevented the action of sulfanilamide, and his studies indicated that the action could be duplicated by para-aminobenzoic acid. It was therefore postulated that para-aminobenzoic acid is an essential metabolite in the growth of bacteria. Thus, the action of sulfonamides may be explained on the basis of a competition with para-aminobenzoic acid, the chemical structure of which is quite similar. When the latter is replaced by a sulfonamide, subsequent metabolic activities necessary for the growth and multiplication of bacteria are stopped.<sup>6</sup>

All these findings in themselves are of considerable interest, but they do not necessarily indicate clinical therapeutic applications. In the case of the sulfonamide-inhibitory action of para-aminobenzoic acid, substances supposedly the same or related to the latter are present in exudates and in tissue juices and they, too, tend to prevent sulfonamide action. On the other hand, para-aminobenzoic acid has been found to have no effect either in preventing or in curing some of the toxic effects of the sulfonamides, such as drug fevers and rashes.<sup>7</sup> Another important aspect of the application of para-aminobenzoic acid in human therapy that is not adequately taken into account by some of those who advocate its use, particularly in small and infrequent doses, is the

fact that this substance, as well as pantothenic acid, is completely and rapidly eliminated from the body, there being practically no storage.<sup>8</sup> Thus, in a clinical trial of its effectiveness in the treatment of typhus fever,<sup>9</sup> the doses used every two hours were from five to twenty times the daily doses advocated for the patient with gray hair.<sup>10</sup> Furthermore, when given for long periods and in quantities adequate to maintain significant concentrations in the blood, the possibility of toxic reactions similar to those resulting from sulfonamides or from thiouracil may be anticipated.

Because of the interest aroused by the reports of the effect of calcium pantothenate and para-aminobenzoic acid on the color of gray hair in human beings, Brandaleone, Main and Steele<sup>11</sup> conducted a series of studies designed to clarify the confusion concerning which of these compounds is the more important. Each substance was fed alone and in various combinations with yeast. They found no significant decrease in the gray color of the hair from the use of these substances over a period of six to eight months.

Another concept often ignored by those who enthusiastically advocate the use of vitamin supplements is the great difficulty encountered in attempts to produce specific deficiencies, even in experimental animals. The conditions under which such deficiencies are induced are extremely artificial and require the administration of highly purified diets, often deficient in many substances. In man, specific deficiencies are also extremely difficult to produce or to maintain in those who take anything resembling a normal diet. Furthermore, the addition of vitamins to the normal diet has been shown recently to have no beneficial effect in otherwise healthy individuals.<sup>12</sup>

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#### MASSACHUSETTS MEDICAL SOCIETY



The people have faith in the medical profession. They want medical security, and the majority want the job done through voluntary prepayment health plans sponsored and controlled by the medical profession.

These are the basic conclusions that can be drawn from the results of a recent survey of public opinion in Michigan. The survey was sponsored by the Michigan Health Council and utilized standard scientific sampling methods to obtain an accurate reflection of opinion throughout the state.

Some of the questions and the answers are as follows:

*As a group, do you think doctors of medicine are doing a good job for the public?*

"Yes," 91.6 per cent; "No," 4.2 per cent; and "Don't know," 4.2 per cent.

*In general, what are your "pet peeves" regarding the medical profession?*

"Doctors overcharge," 6.5 per cent; "Doctors keep patients waiting," 4.4 per cent; "Doctors are dishonest," 5.6 per cent; "Doctors lack interest in patients," 1.7 per cent, and "No peeves," 81.8 per cent.

*Is the medical-hospital plan for employees available where you work? If so, do you belong?*

The responses to the latter question were "Yes," 72.6 per cent; "No," 13.9 per cent, and "Don't know," 13.5 per cent.

*If you were asked to choose, which would you prefer?*

*Voluntary prepayment program sponsored by the medical profession.* 33.7 per cent.

*Government-controlled program.* 15.5 per cent.

*Regular insurance.* 13.4 per cent.

*Payment for service at time rendered.* 26.6 per cent.

No preference was expressed in 10.8 per cent.

The answers indicate that the people have confidence in physicians, that they have few complaints, that nearly three quarters subscribe to a medical-hospital prepayment insurance if it is available and

that, when they know there is a choice, they prefer a prepayment medical plan sponsored by physicians.

The Blue Shield is the medical prepayment plan in Massachusetts. Nearly 4000 doctors are already participating physicians, but the support of every physician is needed so that a united front can be presented to the people and so that it can be said, "The job will be done and done right by the medical profession itself."

If you are not yet a participating physician in the Blue Shield, join your colleagues who are already pioneering in this rapidly developing movement. Write to the Blue Shield (230 Congress Street, Boston) today for complete information.

## TREASURER'S OFFICE

The *New England Journal of Medicine* is sent to all fellows whose dues are fully paid. Fellows who have not paid for the current year by March 1 are automatically dropped from the mailing list. To avoid this, it is urged that all fellows pay their dues by this date. Furthermore, the annual refund to district societies is based on the number of payments received in each district by March 1.

ELIOT HUBBARD, JR., *Treasurer*

## DEATHS

**BONNEVILLE** — Alfred J. Bonneville, M.D., of Hatfield, died January 11. He was in his seventy-fourth year.

Dr. Bonneville received his degree from the Medico-Chirurgical College of Philadelphia in 1911. He was vice-president of the Hampshire District Medical Society in 1920 and president in 1921. He was district supervising censor and counselor of this Society from 1922 to 1945. Last year Dr. Bonneville was cited by Governor Saltonstall for his work in civilian defense. He was on the staff of the Cooley Dickinson Hospital, Northampton, and a fellow of the American Medical Association.

His widow and three sisters survive.

**HASLAM** — Frank A. Haslam, M.D., of Allston, died December 31. He was in his eighty-third year.

Dr. Haslam received his degree from the Harvard Medical School in 1885.

His widow survives.

**RICHARDSON** — Chesley A. C. Richardson, M.D., of Somerville, died January 30.

Dr. Richardson received his degree from McGill University, Montreal, in 1904. He was a member of the executive board, chief surgeon and president of the Medical Staff at the Somerville Hospital and a member of the American College of Surgeons.

His widow and a brother survive.

**THOMPSON** — Charles O. Thompson, M.D., of Boston, died January 29. He was in his eighty-third year.

Dr. Thompson received his degree from Columbia University College of Physicians and Surgeons, New York, in 1889. He was a trustee of the Massachusetts College of Pharmacy and a fellow of the American Medical Association.

His widow, a son and a daughter survive.

## MISCELLANY

### ANNUAL MEETING OF WASHINGTONIAN HOSPITAL

The Washingtonian Hospital for the Treatment and Prevention of Alcoholism held its annual meeting on Tuesday, January 9, in the hospital building at 41 Waltham Street, Boston.

In his report on the activities of the hospital during the past year the medical director, Dr. Joseph Thimann, said that 1134 alcoholic patients had been treated, an increase of 6.6 per cent over the admissions of the previous year. In a group of about 300 patients who were given treatment beyond routine detoxication (part-time protection, psychotherapy and so forth), 25 selected patients received the conditioned-reflex treatment. Since this plan of therapy was started at the hospital, in February, 1942, 111 patients have undergone such treatment, and successful results (permanent total abstinence) have been obtained in 70 cases (63 per cent).

Following the business meeting of the Corporation, the secretary of the Abstinence Club contrasted the early years in the hospital's history, when little or no treatment was given, with present-day conditions. Dr. Arthur H. Ward, acting chief of the Out-Patient Department, then described the work of his department, stating that psychotherapeutic interviews had been given to 200 outpatients during 1944.

Three new members were elected to the Board of Directors: Mr. Courtenay Guild, who for many years has been a member of the corporation and interested in the work of the hospital; Dr. John E. Gorrell, assistant director of the Massachusetts General Hospital; and Mr. Henry L. Johnson, of Utica, New York. Dr. Hilbert F. Day was re-elected president, Mr. Amos B. Little, treasurer, and Colonel George B. Stebbins, clerk.

### ONE HUNDRED YEARS IN THE CONSERVATION OF LIFE

In 1842, a young Quaker named Alpheus Phineas Sharp from Winchester, Virginia, was the first graduate of the Maryland College of Pharmacy. Three years later, or just one hundred years ago, he opened a drugstore at Pratt and Howard streets in Baltimore, a store that was destined to develop into the pharmaceutical and biological laboratories of Sharp and Dohme of today. The store was located in a small two-story brick building, and in the transom over the door he placed a painted piece of glass bearing the words **ALPHEUS PHINEAS SHARP — APOTHECARY**. His stock in trade included the standard household remedies of the day, together with imported perfumes, sponges, combs, chemical glassware and other items carried by the drugstore of a century ago. But he filled prescriptions, too, and it was in this field particularly that his ability and knowledge brought to him the confidence and respect of medical men and his brother pharmacists. The business increased and prospered.

In 1852, a rosy-cheeked boy of fifteen came into the store and asked for a position as apprentice. Mr. Sharp liked the eager energy of the boy and apprenticed him. It was the beginning of a lasting friendship and firm business relation, for the boy was Louis Dohme. He cleaned the store, received instruction from Mr. Sharp, carried Mrs. Sharp's market basket, slept in a back room, ate with the family and between times attended the Maryland College of Pharmacy. His hours were from six in the morning to midnight, and his salary three dollars a week. At the college he studied under Dr. Louis Steiner, who imbued him with the conviction that chemistry was the foundation of good pharmacy. He graduated in 1857 and became senior clerk. In 1860 he was made a partner and the firm name was changed to Sharp and Dohme.

The Civil War, with its requirement of large stores of medical supplies, brought further impetus to the growing business. In 1865 the building next to the store was purchased and the manufacture of an extensive line of pharmaceutical products was begun.

In the meantime, Charles, a younger brother of Louis Dohme, had entered the Maryland College of Pharmacy. He graduated in 1862 and later entered the employ of Sharp

and Dohme. His son, Dr. Alfred R. L. Dohme, later became head of the company and is still a director.

A senior clerk of the Sharp and Dohme store at that time, who later became a nationally known figure in pharmacy, was Charles Caspari, Jr. When he later opened his own store, Alfred R. L. Dohme served an apprenticeship with him, and for many years these two men worked together in determining assay methods of drugs that are still official in the *U. S. Pharmacopoeia*. Dr. Dohme became a member of the Revision Committee in 1891 and remained on it for thirty years.

Both Louis and Charles Dohme were presidents of the Maryland College of Pharmacy, and both Charles and Alfred R. L. Dohme were presidents of the Maryland Pharmaceutical Association and the American Pharmaceutical Association. Louis Dohme was a member of the *U.S.P.* Revision Committee, and Charles the chairman of the Board of Trustees of the *U.S.P.* Convention.

During these early years the company's operations were expanding steadily. Branches were established in New York in 1885, Chicago in 1888, New Orleans in 1890, Atlanta in 1893 and San Francisco in 1898, and in other cities as time went on. Many of the products developed half a century or more ago are still widely used today and with their original brand names. Old-time pharmacists will recall the popularity that greeted the introduction of its instantly soluble hypodermic tablets and gelatin-coated pills.

The history of the Mulford Biological Laboratories is equally interesting. The parent organization, the H. K. Mulford Company, had its origin in one of the oldest drug-stores in Philadelphia, having operated on the same site for about one hundred and twenty-five years. One of the earlier proprietors of this store was Joseph P. Remington, who later became dean of the Philadelphia College of Pharmacy. Another was L. E. Sayre, who later became dean and professor of pharmacy at the University of Kansas.

In 1893 world-wide interest had been aroused by diphtheria antitoxin, a new treatment for diphtheria that was then available only from Europe. The Mulford Company also became interested and established the Mulford Biological Laboratories, which produced diphtheria antitoxin in 1894, the first domestic product to be offered commercially in the United States. This entirely new means of treating diphtheria was an epoch-making event in American medicine. It pioneered the way to the development and use of other biologic products for the prophylactic and therapeutic treatment of disease, which have literally saved hundreds of thousands of lives in this country and abroad.

In 1898, the company began the production of smallpox vaccine and developed many of the processes used today in preparing this product. In the intervening years sufficient vaccine for approximately one hundred million vaccinations has been produced.

The list of biological products either developed or first offered commercially by the Mulford Laboratories is long and impressive.

In the fall of 1929 the businesses of both these makers of fine pharmaceuticals and fine biologicals was combined under the name of Sharp and Dohme. During the past fifteen years the company has registered its greatest growth, more than doubling in scope and size. Over twenty-five hundred persons are employed.

More and more emphasis has been placed on research, a new research building housing a large and well-trained technical staff having been completed in 1943. Some of the more recent developments of the Sharp and Dohme laboratories include many familiar brand names. They also pioneered in the synthesis and study of sulfadiazine and sulfamerazine.

These laboratories also developed the commercial process of lyophilizing biologic products, applicable to certain labile biologicals, particularly dried blood plasma, which has been one of the most important single factors in reducing mortality among American wounded in the present war.

Sharp and Dohme has been so closely identified with the health of the nation since 1845 that its anniversary this year surely can find no better words to describe its activities during that time than "A Century in the Conservation of Life."

## TUBERCULOSIS CONTROL IN HOSPITALS

Unsuspecting carriers and spreaders of the tubercle bacillus comprise a numerically small but important minority of the population. Although most general hospitals dislike to re-

ceive known cases of pulmonary tuberculosis for treatment of unrelated conditions, their patients and personnel nevertheless remain under constant threat of tuberculous infection. This condition obtains because simple, adequate measures are not taken by the institution to detect among the employees, staff and persons admitted as patients the presence of unrecognized or unreported tuberculosis. The problem is discussed in a recent paper (Block, R. G. Tuberculosis control in hospitals. *Bull. Nat. Tuberc. A.* 30:321, 1944).

\* \* \*

Few hospitals will accept tuberculosis of the lung as a disease to be treated within their walls except the large public institutions with special facilities for that purpose. Recently private hospitals in Chicago were asked:

Do you admit patients with pulmonary tuberculosis to your hospital for treatment of that disease?

Do you admit patients with known pulmonary tuberculosis to your hospital for treatment of other conditions?

Of the 73 hospitals that replied, 5 answered the first question with "Yes," and 68 with "No"; 25 replied to the second question with "Yes," and 48 with "No" or with comments that amounted to a negative reply. The answers indicated that hospital administrators do not consider the admission of the tuberculous an asset to hospital service. In fact many of them thought this was an attempt to uncover an administrative deficiency.

In a community with sufficient beds available in tuberculosis hospitals this attitude does not hamper phthisiotherapy, although in the past, physicians have been deprived of facilities to hospitalize their patients in this manner. With the increase of surgical treatment this has often proved hampering. In communities with inadequate facilities for the treatment of tuberculosis, failure to exploit all the available space, especially when numbers of general hospital beds were vacant, has seemed unjustified.

### Fear of Infection

The reason for this is the fear of infecting nontuberculous patients and hospital personnel housed under the same roof. This precaution might be justified if the refusal could really lead to a hospital atmosphere free of tubercle bacilli, but that is not the case.

In recent years, since we have become aware of obscure tuberculosis, our distrust of a negative history and physical examination has become deep-seated and justified. Again and again, evidence has shown that any hospital may have patients with unknown and open pulmonary tuberculosis in its rooms and wards, however little the ailment for which these persons were admitted may have to do with pulmonary disease.

### Routine X-ray Films of Chest

Only universal x-ray examinations of the chest of all patients, regardless of the nature of their complaint, could lead to exclusion of the tuberculous. The University of Chicago Clinics and the affiliated Provident Hospital have x-rayed all clinic admissions for some years with most beneficial results. As a method of avoiding contamination, however, this is only part of the necessary effort. As a means of keeping tuberculosis out of hospitals, pre-admission x-rays would lead to an unnecessary increase in the rejection of patients badly in need of care.

Many patients will always enter hospitals without a previous examination, and they cannot be asked to leave if tuberculosis is discovered. Even if a discharge could be effected without harm to the patients, where should they go for treatment? Tuberculosis hospitals could hardly be expected to engage in the treatment of all extrapulmonary, nontuberculous conditions. Sanatoriums are usually not located or staffed for the purposes of general medicine and surgery. Many communities have no facilities specifically intended for the treatment of patients with tuberculosis.

### Danger of Unrecognized Tuberculosis

General hospitals should accept the necessity of housing tuberculous patients. The danger of infection arises from not recognizing their pulmonary infection, as has been the unavoidable fact up to now.

Proper isolation in one wing, floor or section of the building is easily accomplished. At the University of Chicago Clinics this has been done during the past twelve years.

Through knowing who and where our tuberculous patients are we are avoiding the most acute danger of contamination, which always arises where germs are being spread without the knowledge of either the distributor or the recipient.

### Staff Examination

Isolation protects the medical and nursing staff and other employees against infection from the patient. To make tuberculosis control in a hospital complete, however, physicians, nurses, attendants and so forth, have to be protected not only from patients but from each other, and patients have to be guarded against infection from members of the personnel.

Nearly fifteen years ago, when the University Clinics introduced x-ray examination of the chest by roentgenograms for all nurses, the supervisor of the operating rooms and the nurse in charge of the sterilizing room for the newborn were found with active tuberculosis. Neither was aware of her condition. Stereoscopic roentgenograms were then made obligatory for all physicians and nurses on taking employment, with re-examinations every year for those on general duty and every three months for the personnel of the tuberculosis division.

### General Hospital Personnel

Other personnel were exempt from this routine. About a year later, positive sputum findings began to be reported in patients where no other findings suggested tuberculous infection. The clinical findings in most of these patients suggested upper respiratory or bronchitic involvement. The suggestion that an x-ray examination of the chest of the members of the laboratory staff be made was resented by that staff and rejected by administrative officers.

Eventually, it was found that the laboratory worker in charge of sputum tests, a plump and healthy appearing girl, had extensive cavernous tuberculosis with an almost pure culture of acid-fast bacilli in her sputum. She had contaminated the patients' specimens. The embarrassment of apologizing to the patients in question and of revoking the reports to the health department had a most beneficial effect. Roentgen examination of the chest has since been obligatory for all staff members and hospitals employees and has been gratefully received by almost all of them.

### Sincere Effort Needed

Experiences like this may seem extraordinary. The author believes they appear so only because there has been no great drive to uncover tuberculosis in hospital personnel. There can be no cause for the hesitation on the part of the general hospital to put its house in order with regard to tuberculosis other than inertia and the fear of administrative commotion.

A painstaking design and observance of rules governing the diagnosis and isolation of the disease in patients and employees will make it possible with safety to admit tuberculous patients to general hospitals. There is no reason why all this cannot be accomplished by voluntary efforts. It is obvious from our newer experience with tuberculosis that such hospitalization is one of the great necessities to achieve the basic aim of all medical endeavor — the saving of human life. — Reprinted from *Tuberculosis Abstracts* (January, 1945).

### NOTE

The following appointments to the teaching staff at Harvard Medical School have recently been announced: Henry Merton Baker, of Boston (A.B. Washington Missionary College 1918, M.D. College of Medical Evangelists 1922), instructor in psychiatry; Clifton John Bennett, of San Francisco (A.B. University of California 1938, A.M. University of California 1940, M.D. Johns Hopkins University 1943), assistant in surgery; Frances Jones Bonner, of Greensboro, North Carolina (A.B. Bennett College 1939, M.D. Boston University 1943), assistant in neurology; William Charles Bridges, of Tacoma, Washington (S.B. University of Washington 1936, M.D. Yale University 1940), research fellow in medicine; Ellen Brown, of Berkeley, California (A.B. University of California 1934, M.D. University of California 1939), research fellow in physiology and fellow of the Commonwealth Fund; Francis Ferenc Foldes, of Boston (M.D. University of Budapest 1934), assistant in medicine; Lorye Edward Hackworth, of Sheffield, Alabama (S.B. Florence, Alabama, State Teachers College 1936, S.M. University of Alabama 1938, M.D. Harvard University 1943), assistant in surgery; Elena Jacoby

Hoffman, of Santiago, Chile (M.D. University of Freiburg 1928) research fellow in physiology; Francisco Lachnit Hoffmann, of Santiago, Chile (M.D. University of Chile 1928) research fellow in physiology; Albert Aurelius Hornor, of Brookline (A.B. University of Virginia 1907, M.D. Harvard University 1911), instructor in tropical diseases; Lucie Ney Jessner, of Cambridge (Ph.D. University of Frankfurt 1920, M.D. University of Königsberg 1926), instructor in psychiatry; Robert Harris McCarter, of New York City (A.B. Princeton University 1938, M.D. Jefferson Medical School 1942), assistant in psychiatry; Frank Lothar Plachte, of Boston (Ph.D. Boston University 1942, M.D. Harvard University 1943), research fellow in pediatrics; Robert Maurice Ravven, of Waban (A.B. Harvard University 1939, A.M. Harvard University 1940, M.D. Harvard University 1944) assistant in psychiatry; Sidney Seymour Sobin, of the University of Michigan (S.B. University of Michigan 1935, A.M. University of Michigan 1936, Ph.D. University of Michigan 1938, M.D. University of Michigan 1941), research fellow in physiology and fellow of the National Research Council; Malwina Stock, of Boston (M.D. University of Lausanne 1939), assistant in psychiatry; Paul Francis Ware, of Newton Center (A.B. Holy Cross College 1938, M.D. Harvard University 1943), assistant in surgery; James Wendell Watson, of Grand Island, Nebraska (S.B. California Institute of Technology 1939, M.D. University of Pennsylvania 1943), assistant in psychiatry; Louis Weinstein, of Brighton (S.B. Yale University 1928, S.M. Yale University 1930, Ph.D. Yale University 1931, M.D. Boston University 1943), assistant in infectious diseases; Henry Wermer, of Brighton (M.D. University of Vienna 1936), instructor in psychiatry; and James Martin Woodall, of Boston (A.B. Mercer University 1922, M.D. Harvard University 1930), instructor in psychiatry.

### BOOK REVIEWS

*Radiation and Climatic Therapy of Chronic Pulmonary Diseases: With special reference to natural and artificial heliotherapy, x-ray therapy and climatic therapy of chronic pulmonary diseases and all forms of tuberculosis.* Edited by Edgar Mayer, M.D. 8°, cloth, 393 pp., with 46 illustrations. Baltimore: Williams and Wilkins Company, 1944. \$5.00.

This volume was written by twenty-two collaborators and edited by Dr. Edgar Mayer, long a student of light therapy in pulmonary tuberculosis. The book deals with artificial light, solar radiation, climatotherapy, x-ray therapy and, finally, surgical versus conservative treatment of bone and joint tuberculosis. The concluding chapter is a résumé by the editor of the effects of climatic, x-ray and light therapy on chronic pulmonary diseases and all forms of tuberculosis. In the first chapter, the editor states that he incorporated both skeptical and enthusiastic reports, although an attempt was made to appraise both groups quite objectively. He further agrees that, in some chapters, the deductions are based too frequently on clinical impressions and uncontrolled observations. The reviewer keenly appreciates this point, since many problems relating to the biophysics and physiology of radiation are as yet little understood and await further biophysical as well as clinical study.

The chapters covering the physics of light radiation, especially the one on the physiologic action of light, contain a great deal of valuable information and present to the reader up-to-date information on the effects and dangers of light therapy. Sources of light from the sun, the carbon-arc lamp, the quartz mercury-vapor lamp and the cold quartz lamp are adequately discussed from the physical angle, as well as from the point of view of biophysics and therapeutics. X-ray therapy is recommended in some nontuberculous diseases of the chest, such as actinomycosis, carcinoma and unresolved pneumonia; it is considered beneficial in some extrapulmonary forms of tuberculosis, dubious in tracheobronchitis, and dangerous in pulmonary tuberculosis. The influence of the climate and weather on the human organism in health and in disease is considered in detail, as is climatic therapy of nontuberculous chronic pulmonary diseases. Finally, an attempt is made to evaluate surgical versus conservative treatment in bone and joint tuberculosis.

Dr. Mayer has been in the forefront the past two decades as a student of light therapy. The pooling together in one

book of the experiences of twenty-two eminent men in the field of light therapy makes this book a "must" on the library shelves of anyone interested in tuberculosis and chronic pulmonary diseases. Skeptics will find much, as the editor has pointed out, that is unscientific or empiric. Yet, the text, with its many illustrations, contains a large amount of material that is useful and fundamental for an understanding of present-day knowledge concerning these forms of therapy. The book brings into fruition the many years of laboratory and clinical study by the collaborators as well as by the editor. Although it constitutes a summary of a controversial subject, the book adds a welcome chapter to medical literature.

*Bacterial Infection: With special reference to dental practice.* By J. L. T. Appleton, D.D.S., Sc.D. Third edition, thoroughly revised. 8°, cloth, 498 pp., with 86 engravings and 5 plates. Philadelphia: Lea and Febiger, 1944. \$7.00.

This is a real textbook of dental bacteriology. The author lays out the broad general basis of bacteriology and immunology in the early chapters, drawing abundant example and application from dental theory and practice. It is therefore hardly a text for teachers who give dental students a course in general medical bacteriology and then leave to uncritical clinicians the special application.

As the title implies, much of the subject matter consists of a discussion of infection and the factors affecting its occurrence. The author's discussions are brief and pointed, with references to more extended reading for the unconvinced. Unfortunately, the references themselves are not always convincing.

If courses could be radically revised as soon as a vital new text appears, this book would gain quick acceptance as a text. Until then it will serve as a useful and stimulating source-book and one whose usefulness is not limited to the dental bacteriologist.

*Infections of the Peritoneum.* By Bernhard Steinberg, M.D. With a foreword by Frederick A. Coller, M.D. 8°, cloth 455 pp., with 45 illustrations and 21 tables. New York: Paul B. Hoeber, Incorporated, 1944. \$8.00.

This book, which "it is hoped will be read by the practitioner," will find, nevertheless, a more sympathetic understanding among those in the vanguard of scientific progress. Although the subject is comprehensively dealt with, the special feature of this volume is the presentation of data gathered over many years from the author's own research efforts.

The evidence deduced by the author from these data may be summarized briefly as follows: Peritonitis is a rapidly diffusing infection of the peritoneal cavity in which the exudate obtained by needle puncture is of considerable diagnostic and prognostic value. In the early stage, the average oil-immersion field shows none to 6 free bacteria, whereas the small to moderate number (average, 4000 per cubic millimeter) of neutrophilic polymorphonuclear leukocytes, which make up 85 to 90 per cent of the cells, contain 1 to 10 ingested bacteria, usually of a single species. In the moderately advanced stage, these leukocytes increase to from 60,000 to 250,000 cells per cubic millimeter, the number of free bacteria increases, and a mixed flora may be present. In the late stage, exfoliated mesothelial cells, many of which are degenerated, increase, often to 20 per cent of the cell count; the polymorphonuclears show a high proportion of stab forms and contain many phagocytosed bacteria; the leukocytes decrease in number, many being degenerated; and 10 or more bacteria, almost always more than one species, are seen free in each oil-immersion field. The quality of the defense is reflected in the richness of leukocytic mobilization, the freedom of the leukocytes from degenerative changes, the effectiveness of the phagocytosis of bacteria, the absence of red cells and the relative absence of mesothelial cells. Virulence of the organism and resistance by the host alter these features in varying directions. The safety of needle puncture is stressed and its value in diagnosis will not be disputed by anyone who has had some experience with it in doubtful cases.

The second specific contribution discussed in this volume is the intraperitoneal administration of "coli-bactragen." This is a mixture of a specially prepared colon-bacillus vaccine, aleuronat and gum tragacanth in salt solution and is recommended for mobilization of the polymorphonuclear leukocytes

in the early stages of peritonitis and as a prophylactic against peritonitis in bowel surgery. The clinical evidence for the therapeutic virtues of coli-bactragen is not extensive enough to be convincing, and the author is duly cautious in his claims for its value.

Many interesting experimental data are presented on the peritoneal defense against infection and the value of various therapeutic agents, such as morphine, pituitary extracts and posture. The conclusions reached on the whole reflect the principles guiding surgeons whose therapy is based on critical appraisal of the scientific evidence. Exception may be taken to the impression left by the author that antisera for colon-bacillus and gas-bacillus infections have a demonstrated clinical therapeutic value. Exception may also be taken to the author's interpretation that statistical evidence does not prove the usefulness of sulfonamides in abdominal surgery (penicillin is not mentioned).

One encounters statements of doubtful validity here and there: "The serum protein becomes concentrated as a result of greater nitrogen catabolism" (page 77); "For the duration of the first few days of peritonitis morphine sulphate will control pain and intestinal distention" (page 214) (there is no good evidence that morphine will control distention); "The incidence of pulmonary complications can be reduced appreciably by frequent inhalations of carbon dioxide" (page 214) (the value of carbon dioxide for this purpose has not been demonstrated, and its use has been abandoned by clinics that were among the first to recommend it). On page 241 the author recommends coli-bactragen in conjunction with the operative treatment of gonorrheal peritonitis; this implies that operative treatment has a place in the therapy of such cases, which is not generally accepted. The author's discussion of shock reflects the widespread fallacy that hemoconcentration is a characteristic feature of shock (it should be evident that hemoconcentration is present in burns and other states in which plasma loss predominates but not in conditions in which whole blood is lost, for example, in hemorrhage, or in which no blood is lost, for example, severe generalized infections).

There is much that is repetitious in this volume, but the reviewer believes that this and a tendency to prolixity are defects that a further edition could remedy. Perhaps the author, having in mind the student and the immature practitioner, may regard such criticism as irrelevant. In any case, the book has considerable merit, not the least of which is a splendid and comprehensive bibliography following each chapter.

*Physical Medicine in General Practice.* By William Bierman, M.D. 8°, cloth, 654 pp., with 310 illustrations and frontispiece. New York: Paul B. Hoeber, Incorporated, 1944. \$7.50.

The Government has rationed food, clothes and transportation but not words. Rationing of the last was left for the author of this book. Dr. Bierman's concise style of writing and his economy of words stood him in good stead in producing the present volume. In a relatively limited space he has covered practically the entire field of physical medicine. The thoroughness that characterized his previous works, in which he dealt with single subdivisions of this subject, such as fever therapy and short-wave current, has been retained in a measure in this more general book. It is regrettable, however, that electrophysics is not treated so consummately as are the physiologic effects produced by the various physical measures. By way of an illustration, a brief discussion of such a basic matter as the electron theory of matter and the relation of electricity and magnetism, which forms the basis of induction, is omitted. Nor is it clear why he saw fit to treat the testing of the neuromuscular units for the reaction of degeneration and the sinusoidal and faradic currents, as well as static electricity, under the main heading of "Galvanic Current." But these points are of minor importance and will probably be corrected in subsequent editions, which will undoubtedly be numerous, since the text as a whole is meritorious.

The book covers the usual subjects that are treated in similar works, such as, thermotherapy, phototherapy, electrotherapy, hydrotherapy and electrodiagnosis. In addition it contains chapters on massage, exercise and occupational therapy, subjects with which the general practitioner, as a rule, is not sufficiently familiar to derive from them the great advantage that they offer in the treatment of numerous injuries and certain forms of paralysis.

The final quarter of the book, which is devoted to a discussion of the treatment of specific diseases commonly affecting the systems and structures of the body, will be of inestimable help to the general practitioner provided he has familiarized himself with the preceding chapters, which treat the fundamentals of physical medicine.

Numerous detailed drawings and an appendix covering specifications for physical-therapy equipment are additional features of value.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Segmental Neuralgia in Painful Syndromes.* By Bernard Judovich, M.D., instructor in neurology, Graduate School of Medicine, University of Pennsylvania, clinical instructor in neurology, Women's Medical College, and chief of Neuralgia Clinics, Philadelphia General Hospital, Graduate Hospital, and Women's Medical College Hospital, Philadelphia; and William Bates, M.D., professor of surgery, Graduate School of Medicine, University of Pennsylvania, consulting surgeon, Babies' Hospital and Philadelphia Home for Incurables, and consulting general surgeon, Wills Hospital, Philadelphia. With a foreword by Joseph C. Yaskin, M.D., professor of neurology, Graduate School of Medicine, University of Pennsylvania, Philadelphia. 8°, cloth, 320 pp., with 178 illustrations. Philadelphia: F. A. Davis Company, 1944. \$5.00.

This monograph on a subject formerly known as intercostal neuralgia emphasizes the clinical and therapeutic aspects of segmental syndromes. The clinical value of tenderness is stressed, and much space is devoted to therapy, especially the technic of nerve infiltration. Abdominal-wall neuralgias and other conditions often mistaken for visceral organic disease are thoroughly discussed. Current literature has not been utilized in the writing of this monograph, but it is well illustrated and a number of case histories are inserted in the text.

*Artificial Pneumothorax in Pulmonary Tuberculosis, Including Its Relationship to the Broader Aspects of Collapse Therapy.* By T. N. Rafferty, M.D., with an introduction by Henry S. Willis, M.D., superintendent and medical director, William H. Maybury Sanatorium, Northville, Michigan. 8°, cloth, 192 pp., with 26 illustrations and 14 tables. New York: Grune and Stratton, 1944. \$4.00.

The purpose of this monograph is to compare and evaluate existing standpoints and practices in the use of artificial pneumothorax in the treatment of pulmonary tuberculosis. The book is divided into three parts: general considerations, the choice of cases and management of the procedure.

*Technic of Electrotherapy and Its Physical and Physiological Basis.* By Stafford L. Osborne, M.S., Ph.D., assistant professor, Department of Physical Therapy, Northwestern University Medical School; and Harold J. Holmquest, B.S., B.S. (M.E.), lecturer in applied physics, Department of Physical Therapy, Northwestern University Medical School. 8°, cloth, 780 pp., with 240 illustrations and 72 tables. Springfield, Illinois: Charles C Thomas, 1944. \$7.50.

This textbook is intended to provide a sound physical and physiologic rationale for the technic and application of electrotherapy; it is not intended to replace clinical textbooks but should be used to supplement such treatises. The work is based on lectures given for the past sixteen years at Northwestern University Medical School. The subject matter is divided into four parts: effects and technical application of direct current; electrical muscle stimulation; radiation; and high-frequency currents. The book is well documented and printed in a good type.

*The Neurosurgical Patient: His problems of diagnosis and care.* By Carl W. Rand, M.D., clinical professor of neurological surgery, University of Southern California School of Medi-

cine. 8°, cloth, 576 pp., with 121 illustrations. Springfield, Illinois: Charles C Thomas, 1944. \$4.00.

This new book is based on clinical discussions with students of the neurosurgical department of the Los Angeles County General Hospital, where medical students are assigned cases for review. The discussions are given in a conversational rather than textbook style, and complicated technical terms have been avoided. Informal clinics on fifty-four different subjects are presented in four sections: the spine, head injuries, the brain and miscellaneous conditions.

*The Pathogenesis of Tuberculosis.* By Arnold R. Rich, M.D., associate professor of pathology, Johns Hopkins University School of Medicine. 4°, cloth, 1008 pp., with 89 illustrations, 20 tables and 4 charts. Springfield, Illinois: Charles C Thomas, 1944. \$10.50.

This important new book presents the basic factors and principles that influence the occurrence of tuberculous infection or determine its progression or arrest. The work is well documented, and a list of 1417 selected references is appended to the text. The book is well printed, with a good legible type on good paper.

*Rebel Without a Cause: The hypnoanalysis of a criminal psychopath.* By Robert M. Lindner, Ph.D., United States Public Health Service (R), psychologist, United States Penitentiary, Lewisburg, Pennsylvania, and lecturer in criminology, Bucknell University. With an introduction by Sheldon Glueck, LL.B., Ph.D., professor of criminal law and criminology, Law School, Harvard University, and Eleanor T. Glueck, Ed.D., research criminologist, Law School, Harvard University. 8°, cloth, 296 pp. New York City: Grune and Stratton, 1944. \$4.00.

This volume portrays the basic characterologic factors in the life of a young criminal and reconstructs the mental history of an abnormal personality from earliest infancy through a perverted law-breaking boyhood to young manhood in a penitentiary environment, as revealed through a combined technic of psychoanalysis and hypnosis.

*Lippincott's Quick Reference Book for Medicine and Surgery: A clinical, diagnostic and therapeutic digest of general medicine, surgery and the specialties, compiled systematically from modern literature.* By George E. Rehberger, M.D. Twelfth edition. 4°, cloth, 1460 pp., with 305 illustrations. Philadelphia: J. B. Lippincott Company, 1944. \$15.00.

This standard reference work, first published in 1920, has been thoroughly revised and brought up to date. The sections on gynecology and genitourinary diseases have been entirely rewritten. The list of drugs has been revised in accordance with the twelfth revision of the *United States Pharmacopoeia* and the seventh edition of the *National Formulary*. The book is divided into eleven parts, dealing with different fields of medicine, and each disease or disorder is arranged alphabetically and is described clinically, its diagnosis, etiology, prognosis and treatment being considered in this order. All material is made available through a comprehensive index. This volume should prove valuable as a ready reference work for the general practitioner.

## NOTICES

### BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in the Main Lecture Room of the Harvard Biological Laboratories on Wednesday, February 21, at 8 p.m.

#### PROGRAM

- A Study of Fibrin with Acid and Basic Dyes. Drs M. Singer and P. R. Morrison.
- Use of Stains in Electron-Microscope Investigation of Protein Structure. Miss M. A. Jakus.
- Double Refraction of Flow as a Method for Studying Long Molecules. Dr. J. T. Edsall.
- Some Recent Advances in Radioactive Tracer Technics. Dr. R. D. Evans.

(Notices continued on page xxii)



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## THE HERNIATED INTERVERTEBRAL DISK\*

### An Analysis of 400 Verified Cases

JAMES L. POPPEN, M.D.†

BOSTON

IN THE last ten years considerable material has appeared in publications indicating that the presence of herniated intervertebral disks is not a myth but a proved entity, producing a train of symptoms and signs that are as characteristic as are those of renal colic or appendicitis. As is so true of all new developments, there are always those who are overenthusiastic in the treatment of this disease and those who are skeptical about it.

It is astounding to find that so many proved ruptured disks have been discovered in such a comparatively short time. Inasmuch as it is known that this condition was present since man first assumed the upright position, and that many patients with the now characteristic group of symptoms of a herniated disk did quite well on conservative measures, one must wonder whether or not much of the surgical interference that is now instituted may not be superfluous or even unjustifiable. It is with this in mind that 400 operatively proved cases, in which eighteen months to ten years have elapsed since surgical intervention, have been studied.

An interpretation of one's results cannot be entirely unbiased, and what one surgeon would consider a good result may be judged a poor result by another. All factors must be weighed carefully, such as the personal factor, — the surgeon, industrial surgeon and employee, — the discomfort and disability of the patient before operation as compared with his postoperative symptoms, the ability of the patient to carry out his usual occupation, and his wage-earning capacity. This survey was made on the assumption that most patients are honest, and therefore considerable reliance was placed on the patient's statements whether they considered the results satisfactory. If, however, a patient thought that the result was satisfactory but the facts indicated that he was not back at his usual occupation because doing so resulted in considerable low-back discomfort and necessitated frequent absence from

work, this result was certainly not satisfactory from the industrial surgeon's or employer's standpoint. The patients were checked personally, but they were also requested to answer a questionnaire that gave additional information. In this manner it could be determined with reasonable accuracy whether the operative procedures instituted were justifiable in each case.

There can no longer be any skepticism concerning the presence of the herniated disk and its actual participation in the production of low-back pain and sciatica. There is, however, no question that the time and type of treatment to be instituted are still somewhat vague. For this reason one must not be too decided in his opinion about the proper treatment in a given case until a thorough history has been taken and a complete physical examination, including a bone and joint as well as a neurologic survey, has been made. The laboratory studies should include the usual blood and urine examinations, and roentgenograms of the lower spine and sacrum should be made. These studies usually rule out the more frequent causes of low-back pain with sciatica, such as osteoarthritis, metastatic malignant bone lesions, angiomas of the bone, osteomyelitis, old compressed fractures, Marie Strümpell arthritis, diabetic neuritis, syphilis, and postherpetic neuralgia — evidenced by segmental scars on the skin.

Spinograms should not be used in every case. Certainly, if all the studies have been normal, in the presence of a typical history of a herniated disk as well as typical neurologic findings, it is usually safe to carry out an exploratory operation. Roentgenograms with a contrast medium (oxygen is used exclusively at the Lahey Clinic) should emphatically be made, however, in the following four types of case. The first group comprises patients who have severe sciatica that has not responded to conservative measures in three weeks. If a large defect is present, an exploratory operation is indicated. If a small or no defect is present, one may justifiably continue conservative measures. The second group includes those in whom either the history or the

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†Neurosurgeon, Lahey Clinic.



findings are atypical. The third group is comprised of patients with low-back pain in whom a fusion is contemplated, unless exploration is to be carried out at the time of fusion. The fourth group is formed of patients in whom roentgenograms of the lumbar spine show marked degenerating changes with spur formation.

The study of the 400 cases was instructive because of the fact that the histories were uniformly characteristic. The physical findings varied considerably, depending entirely on the time the patient was examined and whether the condition was in an acute, subsiding or quiescent state. During the quiescent stage the findings in many cases were absolutely normal. Since, therefore, the patients were examined in varying stages, the percentages quoted in the findings must necessarily be different than would be the case if every patient had been examined only during the acute stage.

#### CLINICAL DATA

##### *Frequency*

This series represents 8 per cent of the patients who entered the clinic with the outstanding complaint of low-back pain, with or without sciatica. This emphasizes the point that even though the herniated disk is an important link in the chain of conditions that cause low-back pain and sciatica, it is by no means the predominant one.

##### *Etiology*

It is of interest that 7 patients belonged to families several members of which had had herniated disks. In one family there were two sisters and one brother; in another, two brothers and sisters. A history of injury was given in 65 per cent of the cases. It is significant that the usual account of injury was that of a sudden lifting strain during which the patient felt a snap in the low back and immediately experienced either a numbness and tingling in one leg or a sudden, severe, sharp pain. In many cases, however, the paresthesia or pain did not come on until several hours or days later. It is somewhat difficult to explain why ruptured cartilages do not follow severe injuries such as compression fractures or dislocated fractures of the spine. It appears that actual rupture may take place into the crushed bodies rather than posteriorly, and that during the period of convalescence actual bony union takes place, incorporating the injured disk, and in that manner prevents later herniation.

There can be little question that rupture of disks occurs most frequently at the site of greatest mechanical stress and strain in both the cervical and lumbar regions. The fact that 68 per cent of the cases occurred in males and 32 per cent in females also tends to favor trauma, especially since 84 per cent of the cases occurred in patients between the ages of twenty and fifty and about equally divided in these three decades. Sixty-five per cent were

manual laborers and 35 per cent professional workers. In only 6 per cent of the patients were there demonstrable anomalies, such as spina bifida occulta. Abnormally placed facets were frequent.

##### *Subjective Symptoms*

The duration of symptoms varied greatly. There was no accurate way of determining the actual time element, since in all the cases the symptoms tended to occur periodically, lasting from a few days to several months and occurring over a period of up to twenty years.

Recurrent low-back pain was present in 95 per cent of the patients. It preceded the sciatica in many cases and appeared simultaneously with the leg pain in the remainder, in some cases being located one or two vertebrae higher than the herniated disk. Sciatica was present in every case except 2, in which there was severe mid-low-back pain, coming on at intervals. Both patients proved to have midline ruptures without compression on separate nerve roots.

In 63 per cent of the patients the sciatica was unilateral. It must be emphasized that the pain must be in the sciatic distribution if the disk is at the fourth or fifth lumbar segment, and any pain that is not limited to it must be viewed with skepticism in the diagnosis of herniated disk. Nine patients had pain in the thigh due to herniated disks at the second or third lumbar segment. The exceptions to the rule hold true, however, and in this series 5 patients had associated severe pain in the inguinal region. Seventy-five per cent of the patients complained of pressure paresthesia. Minor motor changes were noted in many cases. Paralysis, however, was the chief complaint of 6 patients. Fifty-two per cent of the patients complained of radiating pain into the leg on coughing or sneezing. Constipation was present in 47 per cent of the series, probably because straining at stool accentuated the leg discomfort. The fact that patients with herniated disks are usually more comfortable while lying down is important to remember, in contradistinction to those with cauda equina tumor, in whom pain is usually less in the upright position.

##### *Objective Findings*

The most constant objective finding was a positive straight-leg reaction, which was present in 90 per cent of the patients when the protrusion was at the third, fourth or fifth lumbar segment. It is safe to say that this test would be positive in nearly 100 per cent of patients if they were examined during an acute phase of the condition. Certainly, if a patient is in a supposedly acute phase and a positive straight-leg reaction is not present, other pathologic factors should be suspected.

Seventy-five per cent of the patients demonstrated definite spasm of the low-back muscles. Localized paraspinous tenderness was present in

80 per cent. Forty-eight per cent had sensory changes in the fifth lumbar or first sacral dermatomes or both. In 35 per cent, list of the spine occurred away from the site of the lesion. In 45 per cent, atrophy of muscle groups — gluteal or calf — or of the extremity from disuse was noted. Fibrillary twitchings were present in 25 per cent. An absent Achilles reflex was noted in 43 per cent, being most frequent with herniated disks at the fifth lumbar segment.

The spinal-fluid studies showed an elevated total protein in only 53 per cent of the patients. Evidence of spinal-fluid block was found in only 2 per cent of the cases. This may be accounted for partly by the fact that in the early group the lumbar puncture was always made in the fifth lumbar space, whereas it is now usually made in the third lumbar space.

Roentgenograms of the lumbosacral spine demonstrated a narrowed interspace at the site of the disk in 15 per cent of the series, localized arthritis (possibly traumatic) in 20 per cent, and an unstable lumbosacral joint in 11 per cent. No characteristic finding indicating a herniated disk was noted in the routine roentgenograms of the spine. Narrowing of the disk space was not an assurance that a posterior dislocation of a disk was present. From these experiences, a normal roentgenogram of the low spine in the presence of a typical history and findings is an additional indication of the probable presence of a ruptured cartilage.

Potentially unstable lumbosacral joints — abnormally placed facets — were present in 6 per cent of the cases. Congenital defects, such as spina bifida, occurred in 6 per cent, indicating at least that congenital malformation demonstrable roentgenologically was not an important factor in producing ruptured cartilages.

#### *Treatment*

The best treatment of herniated disks will remain a subject of debate for some years to come. Conservative surgeons will continue to treat patients much along the same lines as they have treated them in the past — by physiotherapy, immobilization, traction, epidural injections, manipulations and so on. The enthusiasts will, of course, operate on all patients who have symptoms. There are also those who will try to maintain a middle course, attempting to determine which patient should be treated conservatively, which should have simple removal of the disk, and which require a combined removal of the ruptured cartilage and fusion. It is the latter course that would be ideal. The only disadvantage about this position is that with the present knowledge there is no definite rule by which the proper treatment in each case can be determined, and there will not be until at least ten to fifteen years have elapsed so that the results of treatment can be adequately compared. Sufficient time has

elapsed and an adequate number of patients have been treated, however, so that at least certain facts can be kept in mind when the decision concerning treatment is considered.

There is no question that operative procedures were instituted in some cases reported in this series in which conservative measures would have adequately taken care of the situation, but in no case was the condition made worse, except temporarily by postoperative discomfort. Certainly, one should consider the tolerance for pain and the disability of each patient, to decide whether the situation in all its details and findings is typical or atypical, and to make use of these interpretations in deciding on the form of treatment.

Any patient who has had repeated disabling attacks of sciatica necessitating narcotics and who in the previous few months has been unable to work because of a ruptured cartilage should, in my judgment, have operation. When a patient has had mild recurrences of symptoms causing considerable discomfort but not severe enough to discontinue work at any time, he should just as certainly, in my opinion, be treated conservatively. In the latter case, if the neurologic examination shows considerable evidence of root compression, even though the pain is not severe, the patient should have the benefit of surgery.

In any patient who has been disabled with severe pain only for one or two days out of the year, and between attacks is normal, conservative treatment is justified. By conservative measures is meant physiotherapy in the form of heat, massage and postural exercises, rest in bed on a firm mattress and administration of large doses of Betaxin intravenously for a few days. Betaxin is given in an attempt to relieve the associated mechanical radiculitis. Infiltration with procaine locally into the muscle is also of value.

When operation seems indicated, the question naturally arises whether fusion should be carried out at the time the disk is removed. It seems logical that any patient with predominating leg pain (sciatica) and with minor back difficulty whose roentgenograms show no bone changes should have only the disk removed if this is done through a small exposure, whereas in a patient who has predominating back pain, with definitely abnormal facets and evidence of an unstable back, and who has to do hard manual labor, removal of the degenerated cartilage with fusion is indicated. With the latter state, the long initial hospital stay and inability to work may finally prove to be a shorter course in obtaining relief than would have been the case if the disk alone had been removed.

Adequate removal of all the degenerated cartilage should be done in all patients operated on for herniated disk. It is not sufficient to remove only the loose, fragmented portions.

### Postoperative Course

The immediate postoperative course of the patient operated on for a herniated disk is usually smooth, the patient being allowed any liberty he wishes to take. There is no objection to having him stand beside the bed to urinate any time after he has recovered from the anesthetic agent. The back rest is adjusted to any position in which the patient is most comfortable. He is usually up on the seventh postoperative day. The time of getting out of bed after an operation for herniated disk is best left in some degree to the judgment of the patient. Some patients have considerably more discomfort than others and for varying lengths of time after operation. The most annoying postoperative symptoms that occurred in this series were severe spasms of pain in the low back, involving the muscles of the thighs as well. These spasms frequently come on at night, lasting for several minutes and occurring three or four times during the night. They are controlled only by fairly large doses of narcotics. These pains usually occur on the fourth to the seventh postoperative day and last for several days. In 1 case they lasted for several weeks. The incision was reopened in 2 of 10 cases in which these spasms of pain occurred, but nothing was found to account for them except local postoperative swelling of tissue.

Infection occurred in 3 patients. Opening the incision widely and allowing adequate drainage as soon as the infection was noted, with liberal use of the sulfonamide drugs, brought about wound healing in a few days.

The shortest postoperative stay in the hospital was four days and the longest five weeks; the average stay was twelve days.

### Late Results

The late results are analyzed in Table 1.

The relief of sciatica was satisfactory in most of the cases. Residual back discomfort on heavy lifting or sitting in a cramped position for many hours

TABLE 1. Analysis of Late Results.

LATE RESULT	PERCENTAGE OF SERIES
Relief of pain:	
Complete relief of pain . . . . .	65
Complete reduction in sciatica . . . . .	90
Reduction in symptoms:	
75 to 90 per cent . . . . .	20
50 to 75 per cent . . . . .	10
No relief . . . . .	5
Return to usual activity:	
Returned in 1 to 3 months . . . . .	30
Returned in 3 to 6 months . . . . .	30
Returned in 6 to 12 months . . . . .	35
No return . . . . .	5
Unable to do heavy lifting without low-back discomfort . . . . .	60
Able to do everything without discomfort . . . . .	38
Complaint of low-back discomfort when tired . . . . .	40

occurred in almost half the patients. This percentage was not materially altered in those who had also had fusions, who comprised 9 per cent of the series. It must be admitted that of the patients

in whom fusion was performed the predominant symptom was low-back pain, even though associated with sciatica, and that the roentgenograms showed unstable facets with localized reaction at the level of the ruptured cartilage. Two patients complained of severe occurrences of low-back pain in whom spinograms demonstrated midline protrusions at the fourth lumbar space that were verified by exploration. Even though only low-back pain was complained of with no associated sciatica, simple removal of the ruptured cartilage was performed. One patient was completely relieved; the other has had no further severe pain necessitating bed rest, but has been unable to carry on his usual work in a foundry because of low-back discomfort.

The ability to return to work in their usual capacity is encouraging to these patients. This ability depends to some degree on the information that the patient is given before the operation. It must be made clear to him that just because he has had an operation on his back does not mean that it has been weakened and therefore he must be careful of it. Co-operation between the employer, surgeon and patient is highly important. It seems unwise to ask the patient to do a full day's work the day he reports for duty. One must keep in mind that these patients have not used the muscles that are ordinarily exercised in their work and therefore have to be gradually conditioned, just as in any athletic sport in which different groups of unconditioned muscles must be built up gradually. Permanent damage, both physical and mental, can be done by unintelligent conditioning by either the patient or the employer. For this reason postural exercises and physiotherapy are extremely important parts of the postoperative care.

In 15 per cent of the series the patients did not obtain relief; in the majority of cases this was not the result of recurrence. All patients who have persistent leg pain, however, must be suspected of having either a recurrence in the same space or another disk rupture above or below the space where the ruptured cartilage was removed, or a persistent radiculitis. In a few patients posterior spur formation — so-called "eagle-beaking" — of bone from localized degenerative changes takes place, and if the nerve is not adequately decompressed, persistent leg pain will remain.

### COMPLICATIONS

In discussion of this subject emphasis has been placed on the complications that may result from surgery. In competent hands, however, no serious sequelae should follow operation. There were no deaths or paralysis in any of the patients operated on in this series, even though in several cases a root segment was intentionally sacrificed in an attempt to relieve pain. In 1 case injury was unintentional. There were no demonstrable alterations

except slight sensory changes in the lateral aspect of the foot and inability to spread the small toes.

It is important to emphasize what may happen if a patient who has a large ruptured cartilage remains untreated or is treated by nonsurgical methods. In replying to patients who inquired what would happen if operation was not undertaken, it was my original policy to say that so far as I knew, nothing would happen except that the periodic attacks of pain and incapacitation for work would persist for varying periods of time; that, after all, herniated disks had been present for many years in many cases, even though unrecognized except when causing paralysis; and that the present method of proving their presence and taking care of them had been in use only in the last decade. This advice and the logic back of it were unjustifiable, as indicated by the fact that in 6 cases in this series sudden complete paraplegia developed as a result of ruptured cartilage. Of these patients, 2 who had previously always been relieved by careful manipulation by competent osteopaths developed the paraplegia immediately following manipulation; 2 were manipulated by highly competent bone and joint surgeons

and were paralyzed when they awakened from the anesthesia; 1 made a sudden misstep and developed an immediate cauda equina-paralysis syndrome; and 1 gradually developed a cauda equina-tumor syndrome with complete paralysis. In the last case, operation revealed a large disk with an associated adhesive arachnoiditis that completely obliterated the lumbar canal. Even though the protruded cartilages were removed in a relatively short time following the paralysis, many weeks and months elapsed before complete function returned. In 2 of these 6 patients five years after removal of the herniated disk, there is still a marked residual that prevents normal activity.

#### SUMMARY\*

Four hundred proved cases of ruptured intervertebral disk in one or more spaces have been analyzed on the basis of objective and subjective symptoms, and the results eighteen months to ten years after operation have been presented. Hence, no reference to the literature has been made.

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\*This article comprises an analysis of a series of cases seen in a single clinic over the course of ten years and comparative opinions concerning diagnosis and treatment have purposely not been discussed.

## CARDIAC FAILURE ASSOCIATED WITH ACUTE ANEMIA

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IT HAS long been known that anemia has a profound effect on the heart. In 1857, Bamberger<sup>1</sup> pointed out that cardiac enlargement was found in many patients suffering from chronic anemia, a finding that has since been confirmed by many observers. In 1931, Ball,<sup>2</sup> for the first time, demonstrated such enlargement by x-ray and showed that the diameter of the heart returned to within normal limits after the anemia had improved. This finding also has been confirmed by other investigators.<sup>3, 4</sup> In 1939, Ellis and Faulkner<sup>5</sup> studied the hearts of 64 patients suffering from anemia. Of 38 cases examined by x-ray, 20 showed cardiac enlargement, and of 26 that were followed, 18 showed a decrease in the heart size with improvement of the hemoglobin level. It was also found that the anemia tended to produce a lowering of the systolic and diastolic blood pressures. Electrocardiographic studies were carried out. Of 29 patients who were followed, 7 showed abnormal records; in 5 cases these became normal as the blood level increased. With one exception the abnormal records were consistent in that a depression of the ST segment and a flattening or inversion of the T waves in Lead 1 or in Leads

1 and 2 was present. Of the 47 patients studied, 35 suffered from dyspnea, which disappeared in the cases in which the anemia improved. Twenty-one patients showed dependent edema, and in 10 of the 12 patients with edema who were followed, the edema disappeared with the anemia.

Because of the comparative rapidity with which the heart decreases in size once the anemia is relieved, it is generally believed that its enlargement is mainly due to dilatation. Cabot and Richardson,<sup>6</sup> however, found from autopsy material that there was an increase in the weight of the heart in 18 of 19 patients dying of pernicious anemia, and Porter<sup>7</sup> observed a heart weighing 630 gm. in a man dying of hookworm anemia. These findings have been confirmed by animal experimentation. In addition to dilatation and hypertrophy, the heart muscle undergoes fatty degeneration, which is usually most marked in the papillary muscles of the left ventricle, where it produces a speckled appearance under the endocardium, to which the descriptive phrases "tabby cat," "thrush breast" and "tiger-ing" have been applied. These changes in the myocardium have been produced experimentally by Campbell<sup>8</sup> by subjecting animals to low oxygen pressures for long periods. Also, Opitz<sup>9</sup> in 1935 described areas of myocardial necrosis in patients suffering from severe anemia, and Buchner and

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had an apical systolic murmur. The lungs were clear. The hemoglobin was 52 per cent, and 2 days later dropped to 42 per cent, with a red-cell count of 2,520,000. During the hospital stay the patient passed three liquid tarry stools that showed a +++ guaiac reaction. He was given considerable morphine and was transfused, without marked improvement of the anemia. On the 5th hospital day he developed left-sided cardiac failure with pulmonary congestion and expired within 24 hours.

**Autopsy.** The heart weighed 350 gm. There was moderate atherosclerosis of the coronary arteries. Microscopic sections showed moderate myocardial fibrosis. The left lung weighed 1050 gm. and the right lung 900 gm. Both lungs were very boggy and moist. Microscopic examination confirmed the gross diagnosis of marked pulmonary congestion and edema. There was a prepyloric ulcer 0.7 by 0.5 cm. in area with an eroded artery in its base. The large bowel contained much changed blood.

There were 5 other cases in this group. All the patients were over the age of sixty. They showed atherosclerosis of coronary vessels without myocardial infarction at autopsy and presented clinical and anatomic evidence of cardiac failure, which was either initiated or increased by hemorrhage. Four patients had bleeding gastric ulcers, and 1 had a bleeding duodenal ulcer.

### DISCUSSION

Whenever there is severe coronary sclerosis, the myocardium suffers from the result of an actually or potentially inadequate blood supply. From the purely physiologic standpoint, it is obvious that anything resulting in a reduction of the ability of the blood to carry oxygen — reduction in the blood volume, the hemoglobin content or the number of red cells — or in a reduction in the blood pressure that is forcing the blood through a narrowed coronary tree is bound to cause a sudden increase in this inadequacy.

A hemorrhage, regardless of its origin, if severe enough will produce an anemia, a drop in blood pressure and some degree of shock. It might therefore be expected to lead to the signs of decompensation of arteries already having difficulty in carrying out their functions. So far as the heart is concerned, hemorrhage also tends to produce tachycardia, which increases oxygen need and probably per se reduces coronary circulation in relation to volume output.

A frequent but often misdiagnosed cause of hemorrhage in older patients is the erosion of a blood vessel as the result of a duodenal or gastric ulcer. The hemorrhages in these cases are apt to be severe because of the fact that the eroded artery itself is sclerotic and therefore does not easily collapse and thrombose.

It is thus easy to understand why symptoms of inadequate coronary circulation follow such hemorrhages. Why in some cases actual thrombosis of these vessels is found is perhaps harder to understand. It is well recognized that a high percentage of thromboses of the coronary arteries in older patients develop as a result of the rupture of an atheromatous focus into the lumen of a blood vessel. Sudden changes in intra-arterial blood pressure

may possibly account for the rupture of an atherocheuma through its extremely thin endothelial cover into the lumen of the blood vessel and may thus lead to thrombosis.

Severe hemorrhage therefore appears to be more hazardous for the arteriosclerotic subject than for a person with normal arteries. Therapeutically, any means that will combat both profound anemia and a serious drop in blood pressure seems to be indicated, but care must be taken because the same means used to prevent thrombosis in the coronary circulation may be equally effective so far as the vessel producing the original hemorrhage is concerned. Blood transfusion appears to be the treatment of choice, since red cells are thus replaced as well as fluid. Intravenous glucose and saline solutions should be used sparingly, since they tend to reduce the unit oxygen-carrying capacity of the blood while putting additional strain on the heart.

These cases serve to point out the potential danger of having elderly arteriosclerotic patients acting as blood donors. Two cases of probable myocardial infarction following the donation of blood have recently been called to our attention. In a similar manner, these cardiac complications are also apt to occur in elderly patients suffering from traumatic shock or hemorrhage, and preventive means should always be instituted to protect such patients from the cardiac complications described.

### SUMMARY

A series of cases has been presented to emphasize that in patients with severe atherosclerosis of the coronary arteries severe hemorrhage may result in inadequate coronary circulation or coronary thrombosis.

The most frequent cause of these conditions in the present series was hemorrhage from a duodenal or gastric ulcer.

Therapy in these cases is difficult because any method used to prevent the cardiac complications due to hemorrhage may per se lead to further hemorrhage from the original source.

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## CLINICAL NOTE

### BLOODLESS CIRCUMCISION\*

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**A**N OPERATION for circumcision is often brushed aside as unworthy of the efforts of a qualified surgeon, and relegated to an intern or occasional operator without adequate instruction or supervision. The resulting hemorrhage, edema, swelling or even malformation reflects little credit on the medical profession.

The operative steps presented in this paper are designed to obviate these annoying incidents, which sometimes occur even in the practice of the more experienced surgeon. The procedures advocated are based on anatomic facts, so that it will be well to review the essential points involved.

The skin covering the pendulous portion of the penis is remarkable for its thinness, its looseness of connection with the deeper parts of the organ and its lack of underlying adipose tissue. Just in back of the corona the skin is folded inward on itself, forming a free duplicature, — the prepuce or foreskin, — which covers the glans penis to a variable extent. At the constricted neck of the penis, proximal to the corona, the skin is firmly adherent to the underlying tissues, and this firm contact is continued over the corona and glans up to the mucous membrane of the urethra. (The inner layer of the prepuce is often erroneously called "mucous membrane," which it is not.) The outer and inner layers of the prepuce are composed of the same tissues, and when the foreskin is fully retracted the two layers become continuous, without any line of demarcation. Under the skin is a loose layer of connective tissue in which lie the superficial blood vessels, which in the adult may be of considerable size. When the prepuce is over the glans, it has two layers of skin and two layers of connective tissue containing blood vessels. When it is drawn back and held taut, it has one layer of skin and one layer of con-

nective tissue. Contact between the connective tissue and the skin is extremely slight.

Another important fact is not strictly anatomic. Whenever a constriction of the foreskin exists, preventing retraction or producing a phimosis or paraphimosis, the tough, almost rigid ring involves only the skin, and never the underlying connective tissue.

The usual operations of circumcision consist of some form of amputation of the prepuce; others consist of a dorsal slit. In each of these types of procedure both layers of the foreskin are incised at the same time, and consequently two layers of connective tissue, with their vessels, are cut. It is to do away with these unnecessary complications that the following technic is presented.

One first determines at what point he wishes to make his incision through the outer layer of the prepuce. The point having been chosen, the skin, only, is picked up with tooth forceps and a small slit is made in it. The blades of a pair of blunt-ended straight scissors are introduced through the slit and opened. By alternately pushing the scissors forward and opening them, the operator can easily separate the skin from the connective tissue without injuring the latter. This procedure is greatly facilitated if the foreskin is fully retracted and kept tense. If this is prevented by a constriction of the prepuce, the first undermining is done toward the constriction, which is severed from within outward without injuring the connective tissue. The flaps of preputial skin to be removed may be of any size or shape to suit the preference of the surgeon. How they are to be made and how much skin should be removed is not pertinent to this description. If the operator thinks that a dorsal slit is all that is required, it can be made in the manner previously presented.

Two points in this discussion require emphasis. In the first place, both skin layers of the prepuce should never be cut at the same time. In the second place, the skin of the prepuce should never be cut until it has been separated from the connective tissue by blunt dissection. These points may be of slight importance when one is operating on an infant or a small child, but when the patient is an adult they prove themselves worthy of careful consideration.

\*Read by title at the annual meeting of the New England Surgical Society, Boston, September 20, 1944.

## MEDICAL PROGRESS

### DIABETES MELLITUS

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IN THE following remarks on the progress in the treatment of diabetic coma and of pregnancy in diabetes I have confined myself to data from the George F. Baker Clinic for four reasons: they are more favorable and based on larger numbers of cases than are those reported elsewhere; it would be unfair to cite comparative data from other sources, because such reports often represent the results of treatment by many doctors, possibly with different ideas, on different services in a hospital and where, perhaps, the senior members of the staff are able to take a less active part in the management of the individual case; in some hospitals, facilities for laboratory work are inadequate, particularly at night and on Saturday afternoons, Sundays and holidays or the expense of such tests is so considerable that the medical staff is handicapped in securing or feels averse to ordering the same; and, finally, the classification of what diabetic coma is varies according to the author reporting the data. Regarding the last, we believe that a carbon dioxide level of 20 vol. per cent (8.8 millimols per liter) or below is the greatest common divisor. We know the term "unconsciousness" is inaccurate, because so often diabetic patients are unconscious from other causes than ketosis and because the term depends so much on the attitude and tests applied by the examining physician. A recent study<sup>1</sup> of causes of death of 307 diabetic patients in the period 1932 to 1942 on whom autopsies were performed, supports this statement, "The example of a cerebral hemorrhage found at autopsy as a cause of death in a case clinically diagnosed as a diabetic coma is a not infrequent occurrence."

#### DIABETIC COMA

The secret of success in the treatment of diabetic coma is the early and adequate administration of insulin. This is exemplified by experience based on 603 cases treated at the George F. Baker Clinic of the New England Deaconess Hospital between May 23, 1923, and December 31, 1944. Between August 21, 1940, and December 31, 1944, there were more than 9000 admissions for diabetes, with 158 deaths, and among these admissions there were 141 patients in the coma group (blood carbon dioxide 20 vol. per cent or less), with 2 fatalities. Treatment from beginning to end has been essentially the same for all cases except that the first 50 coma patients treated in the earlier period received an average of 83 units of quick-acting insulin in the

first three hours, and the last 141 an average of 206 units.<sup>†</sup> Of the former group 18 per cent died, and of the latter, 1.4 per cent.

During all these twenty-one years, diagnostic laboratory aid has been efficient and prompt — day and night, Saturday afternoons, Sundays and holidays. At a hint of an approaching coma admission the nursing and medical staff, young and old, are alerted, and the rule holds that, after the patient arrives, if there appears a possibility at any time until complete recovery that death might ensue within two hours, two of the older group must be in actual attendance or in close consultation.

The size of the first dose of insulin is usually determined by the clinical estimation of the degree of acidosis, bearing in mind that in a patient with a relatively recent onset of the diabetes, particularly in a child, with acidosis of short duration and with unconsciousness absent, slight or not profound, less insulin suffices than if one is dealing with diabetes or acidosis of long duration and deep unconsciousness. It is in such cases that judgment counts and physicians with large experience dare to give larger doses of insulin than those with somewhat less intimate contact with coma cases. The first dose is usually between 50 and 100 units.

Within thirty to forty-five minutes after entrance, doubt about future treatment is removed because reports of the sugar and diacetic acid in the urine and of sugar and carbon dioxide in the blood are available and, shortly after that, reports of the urinary albumin and sediment and the nonprotein nitrogen of the blood. Subsequent dosage of insulin and its frequency vary with the height of the blood sugar and the depth of the carbon dioxide. Usually the entrance dose of insulin is immediately repeated and again repeated in another hour, that is, about two hours after admission, by which time later reports of the blood sugar and carbon dioxide furnish the therapeutic indications. A few cases recover with a total of less than 100 units, especially if the referring physician has given insulin before arrival, whereas an insulin-resistant patient whose customary daily dose of insulin is 400 units may require 2500 units. As previously mentioned, the average dose administered in the last 141 cases in the first three hours — the period that counts — was 206 units.

Intravenous physiologic saline solution is begun immediately on arrival, because all coma patients

\*Clinical professor of medicine, emeritus, Harvard Medical School; medical director, George F. Baker Clinic, New England Deaconess Hospital.

<sup>†</sup>The average of 216 units for 123 cases in the last group was reduced to 205 units by the addition of 18 cases recently treated. This series included 15 children or patients under 20 years of age several of whom had received large doses of insulin before arrival at the hospital.



are dehydrated. Seldom are less than 2 liters given in the first six hours, and only once has as much as 11 liters of fluid been administered subcutaneously, by vein, by rectum and by mouth in the course of twelve hours, as occurred in Case 15791, that of a patient who recovered under the joint care of Drs. Root and Riseman at the Beth Israel Hospital.<sup>3</sup> This patient, profoundly unconscious, became anuric after the administration of glucose solution. She remained anuric for *nine hours* but recovered when constant intravenous salt solution was given for eleven hours. This patient is not included in our series.

Lavage of the stomach is almost invariably carried out soon after entrance, but the delicacy with which this act must be performed on a patient almost in extremis should be realized. We have never regretted emptying the stomach of a patient in diabetic coma, but despite knowledge gained through practice over many years a reluctance and a delay on various occasions to adopt this procedure have brought embarrassment later when the patient, contrary to our preconceived notions, has vomited unexpectedly large quantities of bloody gastric contents. In the long run it is safer to empty the stomach with a tube, as a rule inserted intranasally, than to have the patient regurgitate and aspirate fluid and undigested food into his lungs.

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in Scotland, Argentina, Chile, England, India, Mexico and Canada as well as in the United States. In the following section an attempt is made to present recent work that has extended knowledge concerning the effects of this diabetes-provoking chemical, which has such a highly selective action and affinity for the beta cells of the islands of Langerhans — all told, they comprise only about 0.007 per cent of the weight of the entire body, the equivalent in weight of a lump of sugar — that it destroys them within a few hours, leaving the remainder of the body intact.

In recapitulation it may be said that alloxan is the ureide of mesoxalic acid. When 200 mg. per kilogram of body weight are injected intravenously into a rabbit, hyperglycemia occurs for one or two hours, followed by extreme hypoglycemia, which, if untreated with glucose or food, usually results in the death of the animal within twenty-four hours. If the animal is prevented from dying in hypoglycemia, diabetes results. Autopsy reveals extensive necrosis of the islands of Langerhans, with destruction of the beta cells but sometimes without notable injury to the alpha cells. The acinar tissue and other parts of the body escape injury unless the dose of alloxan has been excessive. Such animals can be maintained with insulin for over a year, exhibiting severe diabetes with lipemia and acidosis. Similar results have also been obtained with rats and dogs.

Hughes, Ware and Young<sup>13</sup> have produced a state of hyperglycemia followed by hypoglycemia, similar to that which is observed after an injection of alloxan, by the injection of adrenalin and an amount of protamine zinc insulin equivalent to that estimated to be present in the pancreas of a normal rabbit, namely, 10 units per kilogram of body weight. This suggests that the initial hyperglycemia may be due to adrenalin excretion and that the hypoglycemia is not caused by an overactivity of the beta cells, as was once surmised, but rather by the liberation of preformed insulin. This explanation received additional support by the fact that Hard and Carr<sup>14</sup> and others<sup>15</sup> noted that the islands of Langerhans begin to show pathologic change within five minutes after the injection of alloxan. More conclusive evidence was presented by an ingenious experiment of Goldner and Gomori,<sup>16-18</sup> who removed the adrenal glands or destroyed the adrenal medullas of rabbits by intramedullary injections of formalin. A diabetogenic dose of alloxan was then given, and in no instance did initial hyperglycemia develop. Severe hypoglycemia occurred, presumably enhanced by the lack of adrenal counter-regulation factor. They conclude that adrenal stimulation of glycogenolysis is involved in the production of the initial transitory alloxan hyperglycemia. Beta-cell degeneration occurs within the first hour and precedes the hypoglycemia, which usually develops only after four

or five hours. Whenever hypoglycemia develops, diabetes follows if the animal survives. On the other hand, Banerjee,<sup>19</sup> although losing three rhesus monkeys with hypoglycemia following injections of 300 mg. alloxan per kilogram, observed that three others developed diabetes, although their blood sugar levels remained persistently high.

Degeneration of the beta cells with the decrease in insulin production has been demonstrated by insulin assay of the pancreases of Goldner and Gomori's dogs with alloxan diabetes of eighteen, thirty and sixty days' duration. The pancreases of these dogs contained only about one fourth of the 2 to 3 units of insulin per gram contained in those of normal dogs.

Ridout, Ham and Wrenshall<sup>20</sup> have shown in both cats and dogs that the insulin content of the pancreas did not fall appreciably until most islet cells were found by histologic examination to be dead. In other experiments they found that alloxan did not exert a hypoglycemic effect in depancreatized dogs or in dogs previously made diabetic with alloxan. (See also Haist<sup>21</sup> for a comprehensive review including nearly two hundred citations covering the whole question of the insulin content of the pancreas and the factors affecting it.)

Abolition of the initial hyperglycemia subsequent to an injection of alloxan does not prevent the development of alloxan diabetes.<sup>16-18</sup> This is in sharp contrast to the diabetes produced by injections of anterior pituitary extract or by partial pancreatectomy, in both of which the diabetes is prevented if hyperglycemia is counteracted by insulin, phloridzin or starvation.

Bailey and Bailey<sup>22</sup> produced diabetes in rabbits with 200 mg. of alloxan per kilogram body weight in a single dose and also with repeated injections of 40 mg. per kilogram in a succession of seven to thirteen doses over a period of one to three weeks. In the latter animals histologic examination revealed a variety of changes in the islets of Langerhans. Some cells revealed hydropic degeneration, which in many instances is known to be reversible, whereas other cells showed irreversible changes and still others were normal. They report the occurrence of diabetic cataracts in both rabbits and rats and suggest that the administration subcutaneously of 200 mg. of alloxan per kilogram is a feasible method of producing diabetes in rats. Carrasco-Formiguera<sup>23</sup> not only observed a marked variation in the severity of alloxan diabetes in dogs but also reports a recovery from the diabetes. One dog, after exhibiting mild glycosuria and hyperglycemia for a few days as a result of an injection of alloxan, at which time it showed a mildly diabetic dextrose-tolerance test, gave a normal sugar-tolerance test forty-two days after the alloxan injection. This animal was therefore cured after a mild but unmistakable diabetes.

Kennedy and Lukens<sup>24</sup> point out the differences in the susceptibility of individual animals and of

different species to alloxan. Like Hard and Carr and Goldner and Gomori, they found that an animal refractory to alloxan usually does not respond to successive doses. They noted incidentally that animals—dogs, cats and rabbits—under barbiturate anesthesia, when injected with effective doses of alloxan, died; but others<sup>25</sup> have found it possible to produce alloxan diabetes in such rabbits by the injection of a diabetogenic dose of alloxan. Kennedy and Lukens noted no increase in mortality with light ether anesthesia. These authors also emphasize that alloxan is effective in rabbits when given intravenously but ineffective when administered subcutaneously or intraperitoneally, which suggests that it is rapidly altered when in contact with the tissues. In the rat, however, it is effective when given subcutaneously or intraperitoneally.

The rabbits of Kennedy and Lukens excreted 15 to 60 per cent of the available glucose of the diet, and the glycosuria was reduced by fasting. In 4 rabbits there was no evidence of improvement in the diabetes when the diabetes was controlled by insulin. Contrary to the experiments of Bailey and Bailey,<sup>22</sup> they noted no cataracts in rabbits made diabetic by alloxan after a duration of six weeks or longer.

They also observed that alloxan does not inactivate insulin *in vitro*. They state that hydropic degeneration was observed post mortem in the islet tissues of 2 rabbits with diabetes of one to two months' duration. This is ascribed by them to the effect of hyperglycemia on the beta cells that escaped destruction by alloxan.

In an article on the morphologic and physiologic changes of alloxan diabetes in the rabbit, Bailey, Bailey and Hagan<sup>15</sup> emphasize the specificity of action of alloxan, describe the pancreatic-islet changes at intervals after its injection, citing changes even after five minutes, and state that these changes are degenerative from the beginning. Only a certain percentage of alpha cells remain intact, as compared with the lesion in experimental pituitary diabetes, in which there is no destruction of the alpha cells. They observed that the lesions in the kidney of the alloxan diabetic rat were severer than those in the rabbit, all changes in rabbits outside the pancreatic islets being minimal. The lack of cellular response to the necrosis of the islands is remarkable. In almost all other forms of necrosis, neutrophils may be seen at one stage or another. This unusual response to alloxan, therefore, offers a biologic problem of considerable interest. The lesions that were produced by small doses of alloxan resembled all the well-known lesions of the islands in human diabetes. In addition the histologic lesions in the different phases of the blood sugar curve represent one continuous process.

Further discussion of the histologic changes in alloxan diabetes has appeared from the Pathological Department of the University and Western In-

firmary, Glasgow.<sup>26</sup> These authors, too, noted that definite histologic changes can be recognized in the islands in about an hour and may be pronounced in three hours, when some beta cells appear to be necrosed. They also remark:

With doses of 50 mg. per kilogram the beta cells sometimes show degranulation, but little necrosis, at twenty-four hours: the appearances are consistent with abnormal increase of function. After these smaller doses islet changes may be only slight and focal in distribution. Alpha cells are less prone to the necrobiotic changes than beta cells and, from early states, may be enlarged with apparent increase of granules when the beta cells are necrosed or exhausted: this observation suggests some difference in function of the two types of cell. A temporary hyperglycemia almost always occurs in the first two hours where there is any damage to the islets.

Hooded rats were supposed to be resistant to alloxan, but Duff and Starr<sup>27</sup> have found that alloxan injected subcutaneously into these animals in doses of 175 to 350 mg. per kilogram of body weight regularly produced rapid selective necrosis of the islands of Langerhans and characteristic fluctuations of the blood sugar level. Histologic alterations in the islets of Langerhans conformed to those described with white rats, but in addition, a great increase was observed in the activity of mitotic division in the acinar cells during the first twenty-four hours after the injection of alloxan. Hypoglycemic convulsions were not observed. The urine collected during the first six hours was pink, resembling the color that results when alloxan is allowed to evaporate in air. With large doses of alloxan, and sometimes with small ones, the blood sugar rose at times to 800 to 1450 mg. per 100 cc., with death in a state suggestive of diabetic coma, accompanied by massive glycosuria and acetonuria. With smaller doses the animals usually survived for weeks or months without treatment, with blood sugar levels of 300 to 500 mg. per 100 cc. They, too, observed that at one hour after injection histologic changes in the islands were apparent. Most of the destruction occurred in the beta cells, but there were also some necrotic alpha cells. In addition there was a notable increase in the mitotic activity of the acinar cells. With the exception of slight degenerative changes in the convoluted tubules of the kidney and slight fatty metamorphosis of the liver, there were no significant alterations in other organs. Sections of the livers from diabetic animals were lacking in glycogen. Glycogen in the heart muscle was not more than normal, but glycogen in the renal tubular epithelium, especially that of the loops of Henle, was demonstrated in several animals.

Lackey, Bunde, Gill and Harris<sup>28</sup> recall that the glycogen in the heart of a dog or a cat is increased by pancreatectomy. Since both exocrine and endocrine secretions are eliminated by pancreatectomy, they investigated the glycogen problem in rats previously made diabetic with alloxan. The alloxan-treated animals, as compared with the controls, showed a statistically significant increase in glycogen

content of the heart muscle and a statistically significant decrease in that of the liver and skeletal muscle. Rappaport<sup>29</sup> claims that brain slices of alloxanized rats, like those of normal rats, consume more oxygen when glucose is present in the medium than when it is not. The evidence indicates that in the rats suffering from this form of diabetes there is no impairment in the ability of the brain to oxidize sugar.

Koref, Vargos, Rodriguez and Telchi,<sup>30</sup> working in Chile, have produced necrosis of the islands of Langerhans, where others have failed, with the use of alloxantin, which can be regarded chemically as an oxidation product of uric acid or a reduction product of alloxan. This finding has been confirmed by Bailey and Bailey.<sup>31</sup> Alloxan dissolves fairly well in cold water, whereas alloxantin has a low solubility in cold but is fairly soluble in hot water. Another distinguishing mark between the two is that alloxan gives a white precipitate with barium hydrate, and alloxantin a violet one. They therefore used solutions of 1.0 and 2.5 per cent alloxantin at about 50°C. in doses of 70 to 230 mg. per kilogram of body weight. The smaller concentration was the more toxic. Many of the rabbits died before diabetes developed, but others had typical diabetes. Histologic examination showed, as with alloxan, lesions in the islands of Langerhans — cellular degeneration and necrosis, marked diminution of the beta cells and, in cases of long duration, a diminishing amount of islet tissue. They state:

It would appear that alloxantin may produce experimental diabetes, but there are apparently certain differences from the effects of alloxan. First of all there is the paradoxical effect that the lower concentrations, even administered in small doses, are more toxic than the larger doses in higher concentration. This may be explained by the supposition that the alloxantin, like alloxan, is mainly a capillary poison. If such a compound is administered in higher dilution, its diffusibility will be increased, especially in cases of relatively insoluble substances. Consequently it could paralyze more rapidly the capillary system. Higher concentrations with tendency to crystallize may act more slowly, developing rather the symptoms of subacute intoxication. The second fact is that none of the animals treated in our experiments with alloxantin developed hypoglycemic shock, although we could demonstrate that the blood sugar figures reached a very low level.

Thorogood<sup>32</sup> injected 50 rats subcutaneously with 200 mg. of alloxan per kilogram of body weight and found that 10 developed diabetes, 10 were not affected and 30 died. Others<sup>21</sup> observed that 12 of 15 rats developed diabetes with this dosage subcutaneously.

Banerjee<sup>19</sup> reports the production of alloxan diabetes in 3 of 6 monkeys given 300 mg. of alloxan per kilogram of body weight. The remaining 3 died in hypoglycemia.

Recently, Leech and Bailey<sup>33</sup> reported a test for the detection of alloxan in the blood. Using this test they demonstrated that alloxan reaches its highest level at the end of the injection, following which it rapidly decreases, with a complete dis-

appearance in five minutes. This coincides with the finding of Goldner,<sup>16-18</sup> who reports that, if a part of the pancreas is temporarily deprived of its blood supply for five minutes after the injection of alloxan and the temporary blood ligatures are then released, that part of the pancreas escapes injury, showing that the damage occurs within the first five minutes. Leech and Bailey further found the reduced glutathione in the blood was markedly decreased, in some cases to zero, immediately after the injection of alloxan, which suggests an interaction of these two substances. Another sulphydryl compound, — thionine, — in the 2 cases tried, seemed to follow a similar change.

Since the injection of both anterior pituitary extract and alloxan may produce diabetes in animals, it seemed important to find whether alloxan acted through the pituitary gland. Bailey<sup>34</sup> proved that alloxan did not exert its diabetogenic effect in this way, since hypophysectomized rats given alloxan developed diabetes, with characteristic necrosis of the islets of Langerhans.

#### PREGNANCY

Recent publications indicate that the obstetrician and the internist now agree that, whereas the maternal mortality in pregnant diabetic women has been low, the fetal mortality has been high, from 30 to 60 per cent, depending on the duration of the pregnancy.<sup>35-37</sup> Between January, 1936, and January, 1945, a study of 210 consecutive pregnancies in diabetic women was made at the George F. Baker Clinic.<sup>38</sup> In this series 209 mothers and 176 babies survived. An analysis of these cases indicates that a high fetal mortality is preventable.

Maternal, obstetric, chemical and fetal abnormalities characterize pregnancy in the diabetic patient. Thus, diffuse vascular disease and hypovarianism are frequent complications, and more often than not the pregnancies occur in physically and gynecologically aged patients. In the uncorrected course of diabetic obstetrics, early spontaneous interruption of the pregnancy occurs in 25 per cent of the cases, toxemia in 33 per cent, and breech presentations in 33 per cent. Uterine inertia is of common occurrence, and lactation rare. Chemical abnormalities include a low renal threshold for glucose, which favors the development of acidosis and hypoglycemia, water retention in the maternal tissues, amniotic sac and fetus and an imbalance of the sex hormones of pregnancy comprising a rise of chorionic gonadotropin and a fall of estrin and of progesterone, the last having been found in 70 per cent of our cases. Of the fetal abnormalities, overweight occurs in 80 per cent of the uncorrected cases, obesity, edema and splanchnomegaly being contributory factors. Excessive hematopoiesis of the liver and spleen and islet hyperplasia have been observed in nearly all fatal cases. Atelectasis is the



most frequent and important neonatal complication.

Although all these abnormal factors contribute to fetal mortality, the imbalance of the sex hormones of pregnancy appears to be the most harmful factor. In 58 cases in which the sex-hormone balance was normal there were no premature deliveries, 2 per cent of the patients developed toxemia, and 97 per cent of the infants survived. Among the 41 cases with an imbalance of sex hormones, 40 per cent of the patients delivered prematurely, about 50 per cent developed pre-eclamptic toxemia, and only 54 per cent of the infants survived. Estrin and progesterone were administered in 110 cases with the hormonal imbalance. Fifteen per cent of patients delivered prematurely. The incidence of toxemia in patients treated throughout pregnancy dropped to 5 per cent, and fetal survival rose to 89 per cent.

The therapy recommended is as follows: 1 or 2 gr of Armour's thyroid daily, from the beginning of pregnancy; proluton in ascending doses, from the diagnosis of pregnancy to the sixteenth week, 5 mg. three times a week, from the sixteenth to the twentieth week, 5 mg. daily, from the twentieth to the twenty-fifth week, 10 mg. daily, from the twenty-fifth to the twenty-eighth week, 15 mg. daily, from the twenty-eighth to the thirty-second week, 20 mg. daily, and from the thirty-second to the thirty-seventh week 30 to 40 mg. daily; and stilbestrol likewise in ascending doses, from the twentieth to the twenty-fourth week, 10 mg. daily, from the twenty-fifth to the twenty-eighth week, 15 mg. daily, from the twenty-ninth to the thirty-second week, 20 mg. daily, and from the thirty-second to the thirty-seventh week, 30 to 40 mg. daily. The diet should include liberal quantities of carbohydrate and protein; salt should be omitted after the sixth month. Insulin is usually necessary before lunch and supper, in addition to the breakfast dose.

The time for delivery is the thirty-seventh week, and we believe that the method of choice is cesarean section, without medication and under spinal anesthesia.

The welfare of the infant is aided by oxygen incubation, mechanical stimulation, dehydration and drainage.

It does not seem illogical to believe that the vascular disease and hormonal imbalance of the young diabetic woman predispose her to the vascular disease and hormonal imbalance of pregnancy — a prematurely aging patient — and a prematurely aging placenta.

#### STATISTICS

A preliminary and round figure for diabetic deaths in the United States for 1943 is 37,000, a rate of 27.6 per 100,000.<sup>39</sup> New York leads with 43.6, Rhode Island follows with 43.0, and Massachusetts is third with a rate of 39.4. The percentage increase

in the total United States for the three years 1930–1932, as compared with the three years 1940–1942, was 27 per cent. By states, Oklahoma and Arizona led with increases of 48 and 47 per cent, respectively; the higher rates, however, were only 15.2 and 11.9 per 100,000. The increases in New York, Rhode Island and Massachusetts were respectively 40, 27 and 38 per cent.

Rates for the industrial insured cases of the Metropolitan Life Insurance Company for the period 1939–1944 have varied from 27.4 per 100,000 in 1941 to 29.8 in 1940; the rate for 1944 was 27.6.

#### DIABETES ABSTRACTS

Mention should be made of the great contribution to the diffusion of knowledge concerning diabetes that has been afforded by the joint publication of *Diabetes Abstracts* by the American Diabetes Association and the Eli Lilly Company. Four numbers appear yearly. They contain an exceptionally careful summary of all current papers on various aspects of the disease. The time thus saved to the physician is almost incalculable.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31081

#### PRESENTATION OF CASE

A fifty-four-year-old dishwasher was admitted to the hospital complaining of dyspnea, chest pain and rusty sputum.

The patient was well until about one month prior to admission, when he developed a persistent slightly productive cough following an upper respiratory infection. Five days before entry he developed generalized aches and pains, with malaise and a shaking chill. On the following day he experienced a second chill. He noted slight sharp pain in the right chest on inspiration and increasing dyspnea. Three days before entry he began to cough up rusty sputum.

The patient had had urgency and nocturia (two to three times) for several years, associated with difficulty in starting and a diminution in the force of the stream. He had had some dyspnea on climbing one flight of stairs, but there was no history of orthopnea, ankle edema or pain in the legs. He drank six to eight glasses of beer daily and whisky occasionally.

Physical examination revealed a well-developed and well-nourished, slightly cyanotic and dyspneic man appearing acutely ill. The skin was hot and moist. The pupils were somewhat irregular, and the fundi revealed slight tortuosity of the vessels, with arteriovenous nicking. Over the right lower lung field, more marked posteriorly, there were dullness, increased tactile and vocal fremitus, and diminished breath sounds. A Grocco's triangle was present on the left. The heart sounds were poorly heard. A marked aortic systolic murmur, accompanied by a thrill, was heard over the precordium, with maximum intensity about 5 cm. to the right

of the sternum in the second intercostal space; it was transmitted to the right axilla and through to the back on the right. The abdomen was distended and tympanitic. The knee jerks were diminished, and the ankle jerks absent.

The temperature was 103°F., the pulse 110, and the respirations 24. The blood pressure was 100 systolic, 50 diastolic, in the right arm, 115 systolic, 70 diastolic, in the left arm, and 150 systolic, 70 diastolic, in both legs.

Examination of the blood revealed a red-cell count of 3,370,000, with 12.3 gm. of hemoglobin, and a white-cell count of 10,000, with 94 per cent neutrophils, of which 74 per cent were band forms. There were marked toxic granulations in the neutrophils. The urine had a specific gravity of 1.015 to 1.020, with a ++ test for albumin on admission but none thereafter; there was an occasional white cell and coarsely granular cast in the sediment. The stools were negative. The serum nonprotein nitrogen was normal, and the protein was 5.4 gm. per 100 cc., with an albumin-globulin ratio of 1.9. The prothrombin time was 24 seconds (normal, 18 to 20 seconds), and a cephalin flocculation test was negative. A bromsulfalein test showed 15 per cent dye retention. A sputum culture on admission revealed an abundant growth of Type 5 pneumococci, and a culture five days later showed a few beta-hemolytic and many alpha-hemolytic streptococci. Five blood cultures were negative. An electrocardiogram showed slight left-axis deviation, biphasic T<sub>1</sub> and T<sub>2</sub>, flat T<sub>3</sub> and sagging ST segments in Leads 1, 2, CF, and CF<sub>3</sub>, findings consistent with left ventricular strain and hypertrophy.

A roentgenogram of the chest revealed density in the right lower lung field. There appeared to be some widening of the right side of the mediastinum. The left lung field was clear. A repeat film three days later showed considerable density remaining in the right lower lung field; this was definitely within the lung. There was no other change.

Soon after admission the temperature spiked to 106°F., after which it ranged between 101 and 103, with occasional spikes to 104. Respirations averaged about 30. A tap of the right chest yielded slightly viscid, cloudy fluid containing fibrin; there were 50 cells per high-power field, 98 per cent of them being polymorphonuclears. Sulfadiazine therapy was instituted, following which the white-cell count fell to 3800. On the fifth hospital day, sulfadiazine was stopped and penicillin substituted. The white-

\*On leave of absence.

cell count gradually rose to 12,000. A second thoracentesis, on the seventh hospital day, was productive of 650 cc. of viscid cloudy fluid having a specific gravity of 1.020 and a white-cell count of 4300, with 65 per cent polymorphonuclears. A culture of the fluid revealed *Staphylococcus aureus*. On the following day the patient complained of sharp pain on inspiration over the right lower chest, but no friction rub could be heard in this area. Fluoroscopy on the ninth hospital day revealed a wide mediastinum, an active expansile pulsation in the upper chest to the right of the midline, and what

sternum in the upright than in the supine position.

On the fourteenth hospital day a therapeutic test with three 200-r doses of x-ray was begun. The patient showed no subjective change, and the temperature continued to range from 101 to 102°F. Penicillin was stopped on the twelfth hospital day, and 0.1 gm. of digitalis was administered three times daily. A roentgenogram of the chest on the eighteenth hospital day showed the density over the right lower lung field to have largely disappeared. Only a small amount of fluid remained in the right pleural cavity. The heart and mediastinum were markedly dis-

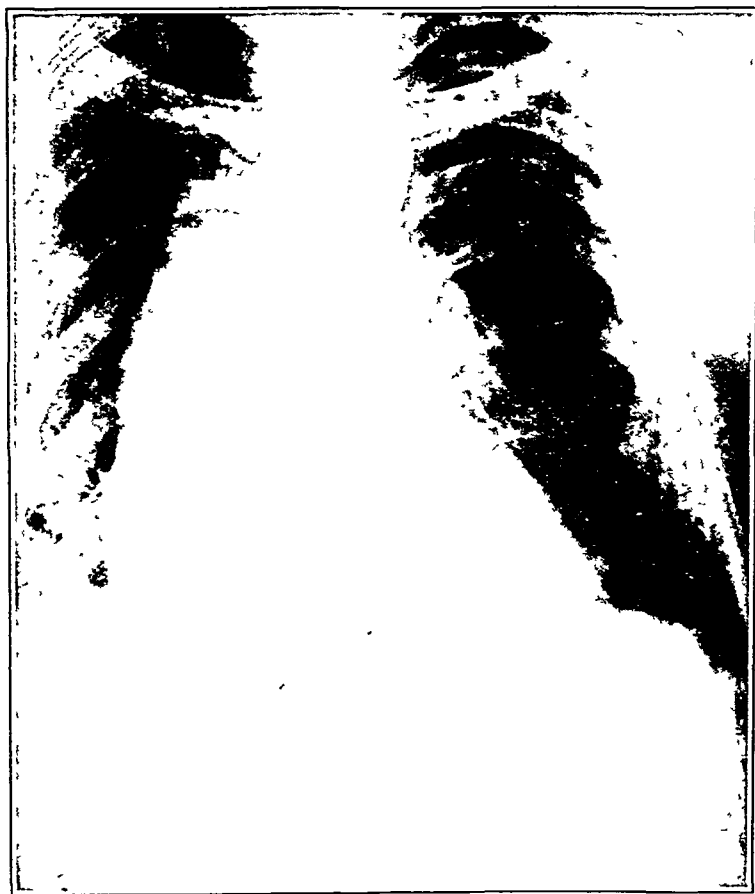


FIGURE 1.

appeared to be collapse of the right lung at the base, with only a minimal amount of fluid. Examination of the chest showed decreased resonance at the right base, with diminished breath sounds and a few rales, especially posteriorly. There was dullness over the hilar region in the right posterior chest. Examination of the heart revealed the point of maximum intensity to be 10.5 cm. to the left of the midsternal line and 1.5 cm. beyond the left midclavicular line in the fifth intercostal space. The loud aortic murmur, as well as the thrill, was transmitted over the whole chest and into the neck, abdomen and back. It was loudest about a centimeter nearer the

placed to the right, and in the lateral view there was a suggestion of collapse of the greater part of the right lower lobe. The heart was enlarged, particularly in the region of the right ventricle. The aorta was tortuous and calcified, but there was no demonstrable evidence of aneurysm (Fig. 1). On the twenty-fourth hospital day, the temperature rose to 103.4°F. and the patient complained of intense pain over the right lower chest on inspiration. The breath sounds over the right middle lobe were absent, and the heart sounds were muffled. Fluoroscopy and roentgenograms of the chest revealed that the pulsations of the heart and aorta were much smaller

-than at the time of the previous examination. A large area of calcification was visible in the valvular area of the aorta, but there did not seem to be any appreciable aortic widening.

On the twenty-sixth hospital day the patient suddenly complained of intense and persistent chest pain; he died two hours later.

### DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: "A fifty-four-year-old dishwasher was admitted to the hospital complaining of dyspnea, chest pain and rusty sputum." It sounds like lobar pneumonia, and the story of the illness immediately preceding entry also sounds like pneumonia.

The urgency, nocturia and so forth suggest that he had prostatic difficulty, but nothing more is said about it. In the story later on we find that he had a normal serum nonprotein nitrogen.

"He drank six to eight glasses of beer daily and whisky occasionally." I shall take that statement at face value, and I must say that it is not a terrific alcoholic history.

It is stated that there were diminished breath sounds with increased tactile and vocal fremitus. I doubt it; at least it does not sound reasonable.

"Grocco's triangle was present on the left." In other words, there was contralateral dullness.

The diminished knee jerks probably were of no consequence. The problem of obtaining ankle jerks in an extremely sick man makes that observation doubtful.

We still have evidence consistent with consolidation of the lungs, which is also consistent with pneumonia, and nothing so far to suggest that this patient did not have pneumonia. There is, however, the possibility of a heart lesion. The findings in the heart suggest calcareous aortic stenosis. The question is whether or not to take seriously the difference in blood-pressure readings in the two arms. To my mind the difference is not great enough, at least on the single observation, to put much stress on the finding.

The white-cell picture, with 94 per cent neutrophils, is certainly consistent with a fairly severe, acute pyogenic infection. Although we are not told what the other 6 per cent were, I assume that they were lymphocytes and that there were no eosinophils and no monocytes. The marked toxic granulations of the neutrophils can be overemphasized, but taken with the differential picture it is strong evidence in favor of an acute pyogenic infection. It is equally strong evidence against infection such as subacute bacterial endocarditis or septicemia without an acute exudative process, such as an abscess or something of that sort.

DR. BENJAMIN CASTLEMAN: The remaining 6 per cent in the differential count was composed of 2 per cent large lymphocytes, 2 per cent small lymphocytes and 2 per cent monocytes.

DR. RICHARDSON: Although there are too many monocytes, the white-cell picture is consistent with and quite suggestive of pneumonia.

I might as well get the anemia out of the way. The red-cell count of 3,300,000 indicates a fairly definite anemia. I should like to point out that red-cell counts are not so accurate as they are thought to be. It is known that, when they are done by well-trained technicians on the same patient and repeated, they can vary as much as half a million or more in either direction. Of course, that does not mean that the error is always going to be that much. One cannot take a single observation too seriously; however, one must assume that this anemia meant something. That brings us down to the hemoglobin. In the general wards of this hospital it is presumably done by the Sahli method, and *one should not be too impressed by the figure 12.3 gm.* The Sahli method is full of snares and delusions—I fear that I am going to be hypercritical, even iconoclastic, about this. The Sahli test may vary as much as 25 per cent if one uses a yellow light, a filter light or daylight. Furthermore, the standards may fade, and although it is desirable frequently to calibrate them, they almost never are calibrated. With a faded standard the reading is obviously too high. This particular blood works out as a macrocytic anemia with a color index of 1.3.

DR. CASTLEMAN: Five days after the first blood examination the red-cell count was 3,800,000; the differential white-cell count was 77 per cent neutrophils, of which 40 per cent were band forms with toxic granules, 12 per cent large lymphocytes, 8 per cent small lymphocytes and 3 per cent monocytes. A red-cell count done two weeks later was 3,600,000, with a hemoglobin of 10.5 gm.

DR. RICHARDSON: That would be a normochromic anemia.

The anemia should be explained, and I find it one of the most difficult things in this record to do. Anemia of course can occur with sepsis, but it usually follows chronic sepsis. One would expect it to be a little slower in developing. It is possible, however, that it was due to chronic sepsis. Anemia due to malignant tumors, provided the tumor is not in the gastrointestinal tract and associated with blood loss, or possibly a nutritional element, shows a considerable degree of regeneration. If one saw a smear with an anemia of that degree and then found numerous nucleated red cells or polychromatophilia with stippling or other evidence of regeneration, it would be suggestive of a malignant tumor. I do not believe that malignant tumor of itself produces anemia of this type. I do not know what the red cells looked like, as a matter of fact, and therefore one has to consider that this anemia may have been due to lack of liver principle or to some nutritional disturbance. The anemia of uremia may produce toxic granules, but we are told later on that the

patient had no uremia. One more point about the hemoglobin: I find that the most satisfactory method of hemoglobin determination, except for photoelectric measurement, is that given by the Tallqvist scale, using one of the old books. I expect that I shall hear a lot more about this statement later on.

DR. J. H. MEANS: I may say at this point that I think you are quite right. One has to add, however, that the person taking it should back up against the window and read it in daylight.

DR. RICHARDSON: It has to be read right away. The paper must be folded over double and the person should have his back to daylight. Using the old scales I can get a fair correlation with the photoelectric determination. It is not a falsely accurate test the way some of the others are.

"An electrocardiogram showed . . . findings consistent with left ventricular strain and hypertrophy." I shall accept that statement and make no further comment.

"Sulfadiazine therapy was instituted, following which the white-cell count fell to 3800." I still think that this story is consistent with an acute infection of the lung that had not resolved.

The fluid in the right lung was not a transudate; it appeared to be associated with infection in the lung and approached a definitely infected fluid of the empyema type, although it had not reached that stage. It certainly was not pus, but it seems as if it might well have been infected fluid.

There appears to be some question of aneurysm in this case, and I know that there is no report in the record of a Hinton test. I do not believe it was aneurysm. I assume that the test was not done or was negative.

DR. JOSEPH C. AUB: It was done and was negative.

DR. RICHARDSON: I suppose they gave him x-ray treatment as a last resort. It must have been a forlorn hope.

As I went over this story the first time, I did not quite gather the time relation. The patient apparently was well until a month prior to admission, and on the twenty-sixth hospital day he died. That means that he was sick for two months. To me this story is one of infection. I have to mention the possibility of aneurysm, but I do not believe that it was present. I believe that this man started off with pneumonia, which did not clear up, that he later had an infected pleura, with perhaps a localized empyema, that still later he had enough obstruction of the bronchus to cause collapse of the right lower lobe and that he ended up with an acute purulent pericarditis. In his heart, I believe that he had a calcareous aortic stenosis and also probably a good deal of calcium in the aortic arch. I do not believe that he had an aneurysm. In view of the length of the history, the anemia that I mentioned is consistent with chronic sepsis. The change in the blood picture in the last five days is difficult to explain, but it might have been an acute process turning

into a chronic condition, perhaps as a result of drug therapy. I have nothing more to say.

I should like to have Dr. Robbins comment on the x-ray films. I might ask him first if he knows the answer; then I shall know how to interpret what he says.

DR. LAURENCE L. ROBBINS: I know the answer.

This is the film that was taken on admission, and all I can say is that the density of the right lower lung field could be due to fluid or to consolidation within the lung. The heart appears to be displaced to the right, and this shadow suggests widening of the superior mediastinum. At a later examination some of the density is definitely due to consolidation; I think, however, that there is still some evidence of fluid in the pleural cavity. The fact that we can see the bronchi suggests that there was a loss of aeration of the alveoli adjacent to the bronchi. Then as we go along a little farther, — if I remember correctly the department was being pushed for an opinion whether this could have been an aneurysm of the ascending aorta, — the process within the lung and the pleural cavity has cleared considerably. The heart and mediastinum remain considerably over to the right side. So far as we could determine at that time there was no widening of the aorta itself but the pulsations were considerably larger than one expects normally; we did not recognize the fact that there was some calcification in the valvular area. It is possible to see a large area of calcification in the region of the aortic valve. The heart has increased somewhat in size between these two examinations, representing a six-day interval. Even knowing the answer, I still cannot explain why the heart, mediastinum and aorta are displaced far to the right side. I do not believe that there is enough disease in the lung to explain this displacement.

DR. AUB: In the fluoroscopic examination the mass displaced to the right, which Dr. Robbins has stressed, pulsated twice in each beat, auricular and ventricular.

DR. RICHARDSON: I do not see much evidence of a localized empyema, but there may still be a localized area of infected fluid. My diagnoses are lobar pneumonia, which was resolving, calcareous aortic stenosis, acute pericarditis and possibly localized empyema.

DR. REED HARWOOD: The fact that this patient was sick for several weeks suggests that possibly he had something in the bronchial tree. Could he not have had a carcinoma of the bronchus to produce this bulge in the mediastinum?

DR. CHESTER M. JONES: Why did he have x-ray treatments?

DR. RICHARDSON: I was wondering about that.

DR. AUB: The patient had a thrill and a murmur as marked as any I have ever felt or heard. They extended almost to the right axilla and were much more marked when the patient was sitting up than

when he was lying down. That was the most striking thing about the examination.

He was first given sulfadiazine, which did not do any good, and then penicillin, which also was of no help; finally we had nothing else to offer except x-ray therapy, because of the remote possibility of Hodgkin's disease.

#### CLINICAL DIAGNOSES

Dissecting aneurysm, with rupture into pericardium.

Resolving pneumonia (Type 5).

Aortic stenosis.

Hemopericardium, with cardiac tamponade.

Massive pulmonary embolism, acute.

Thrombosis: right popliteal and femoral veins.

Resolving lobar pneumonia: right middle lobe.

Pulmonary infarct: left lower lobe.

Cardiac hypertrophy, left ventricular.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy this man presented an unusual picture. The heart was tremendous in size, weighing 800 gm., and showed marked left ventricular hypertrophy due to a marked calcareous aortic stenosis. Superimposed on the calcareous



FIGURE 2. Mycotic Aneurysm of Aortic Valve Located between Aorta and Pulmonary Artery, Bulging into Right Ventricle and Rupturing into Pericardium.

#### DR. RICHARDSON'S DIAGNOSES

Lobar pneumonia (resolving).

Calcareous-aortic stenosis.

Acute pericarditis.

Localized empyema?

#### ANATOMICAL DIAGNOSES

Calcareous aortic stenosis.

Subacute bacterial endocarditis, aortic valve, with formation of a mycotic aneurysm and rupture into pericardium.

stenosis was a subacute bacterial endocarditis that had eroded the aortic wall in two places, one just behind a cusp in a sinus of Valsalva and the other just above the valve and near a large calcareous mass. I wondered if the constant rubbing of the calcareous mass on the aortic intima in this location might have been an added factor in producing the rupture. The perforation opened into the space between the aorta and the pulmonary artery, producing a large mycotic aneurysm, 6 to 8 cm. in diameter, with a tremendous bulge into the right

ventricle just beneath the pulmonary valve (Fig. 2). The aneurysm had invaded the ventricular wall but had not reached the endocardium, and had the patient lived longer, it might have ruptured into the right ventricular cavity, forming an artificial interventricular septal defect. This large mycotic aneurysm had ruptured superiorly into the pericardium, which at the time of autopsy contained a liter of blood. That was not the immediate cause of death, although, if we had found nothing else, we might have interpreted it as such. The enlarged heart shadow seen on the roentgenogram several days before he died undoubtedly was produced by the hemopericardium. The immediate cause of death was a massive embolus that filled the entire pulmonary artery and had extended into several branches within the lungs. These emboli came from thrombi in the right popliteal and femoral veins.

The lungs showed resolving pneumonia of the right middle lobe and a recent infarct in the left lower lobe, which probably occurred after the last x-ray film was taken. Nonhemolytic streptococci were grown from the contents of the aneurysm, from the vegetation and from the blood at autopsy.

DR. RICHARDSON: I made the flatfooted statement that the blood was not consistent with subacute bacterial endocarditis. I should like to modify that remark. I think that the first blood picture was not that of chronic sepsis but of acute sepsis, consistent with the pneumonia; the later blood report could be consistent with subacute bacterial endocarditis.

DR. CASTLEMAN: I cannot be sure when the mycotic aneurysm began, but I believe that it was there the day the patient came into the hospital. It was probably not so large, but it almost certainly had begun. The initial infection that led to the bacterial endocarditis may well have been the upper respiratory one over a month before admission. The hemopericardium occurred slowly during the last days of his life.

## CASE 31082

### PRESENTATION OF CASE

A seventy-four-year-old woman was admitted to the hospital with abdominal cramps and vomiting.

The patient had been in fairly good health until two days prior to admission when, after a light meal, she was suddenly seized with generalized abdominal cramps. This was followed by an episode of vomiting, which relieved the pain. During the night a second attack occurred. The abdominal cramps continued, and she was unable to take anything by mouth without vomiting. During this period, several enemas were productive of hard fecal masses; there was a small spontaneous bowel movement about an hour before admission.

The patient had had a hernia in the left groin since the age of ten. It had never been painful. About thirty years before entry she had attempted to wear a truss, but it was unsatisfactory and soon abandoned. About twenty-five years before admission the patient had had an acute episode of nausea, vomiting and upper abdominal pain diagnosed as gall-bladder disease. She recovered after about two weeks. Since that time she had had mild intolerance to fried and fatty foods and had avoided them. She had never had jaundice or tarry or acholic stools.

The patient required three pillows for sleeping but had never had dyspnea or edema. She had been told that she had high blood pressure and had had an episode of severe epistaxis one year before entry. She had been blind in the right eye for a year and in the left eye for six months, as a result of cataracts.

Physical examination revealed an obese dehydrated woman, vomiting frequently. Bilateral cataracts were present. The lips were cyanotic. The lungs were clear. The heart sounds were faint and irregular, and there was a soft systolic murmur over the pulmonic area. The abdomen was moderately distended, tympanitic and diffusely tender; no peristalsis was heard. A mass the size of a goose egg was present in the left groin and was believed to be a femoral hernia; it was tender and not reducible. Varicosities were present on both legs.

The temperature was 99°F., the pulse 86, and the respirations 24. The blood pressure was 200 to 216 systolic, 90 diastolic.

Examination of the blood revealed a red-cell count of 5,300,000, with 90 per cent hemoglobin, and a white-cell count of 14,400. The urine had a specific gravity of 1.014, with a ++ test for albumin, a + test for acetone and no sugar; the sediment contained innumerable white cells. The serum non-protein nitrogen was 65 mg. per 100 cc., the protein 7.2 gm., and the chloride 93 milliequiv. per liter. The prothrombin time was 23 seconds (normal, 18 to 20 seconds).

A roentgenogram of the abdomen revealed numerous loops of dilated small intestine. There was a shadow of increased density overlying the sacrum (Fig. 1).

After several unsuccessful attempts, a Miller-Abbott tube was passed into the jejunum. The patient was given 6 cc. of Cedilanid intravenously. On the second hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. EDWARD HAMLIN, JR.: Since Dr. McKittrick\* has pointed out in a paper on acute intestinal obstruction that the one most important factor is the flat film of the abdomen, I think that we might start by looking at it.

\*McKittrick, L. S. Diagnosis and management of acute obstruction of small intestine. *New Eng. J. Med.* 225:647-652, 1941.

DR. MILFORD D. SCHULZ: This film was made when the patient first came in, and you can see the widely dilated loops of small bowel. Over the sacrum is a shadow which, if it were in the right upper quadrant, I should call a gallstone. Since it is down over the sacrum I suppose it could be a calcified fibroid. If it were a gallstone I should expect some gas to be present in the liver or in the gall bladder.

in the opening sentence of the paper, "If one excludes strangulated external hernia, the diagnosis of which is easy and the treatment obvious. . . ." Sometimes the diagnosis is not so easy, and the treatment not so obvious.

But one must make a diagnosis. There are numerous factors that one would like to know about, as always in these exercises; some of them are probably



FIGURE 1.

DR. HAMLIN: There are obviously red herrings around, and that shadow is at least a fish.

DR. SCHULZ: It is interesting to know, too, that the gas stops at the dense shadow.

DR. HAMLIN: The diagnosis of small-bowel obstruction is obvious from the recorded physical examination and from the abdominal film. The story seems to lead rather clearly to a consideration of some sort of an incarcerated hernia as the cause of obstruction. Dr. McKittrick, as I mentioned before, in writing on intestinal obstruction, states

not incorporated in the record, but some of them may be. One certainly would like to know more about the history and the character of the pain. Was the pain constant, although crampy in nature? Had it become more persistent, with crampy exacerbations, indicating that perhaps some form of strangulation of the intestine was taking place? It is of tremendous importance to differentiate simple obstruction and strangulated obstruction.

DR. BENJAMIN CASTLEMAN: Dr. Crystal, can you answer any of Dr. Hamlin's questions?

DR. DEAN K. CRYSTAL: We gained the impression that it was crampy pain, the severity of which had not changed during the illness.

DR. HAMLIN: The description by the patient leads one to believe that she was not a good informant.

DR. CRYSTAL: It was rather difficult to get the story.

DR. HAMLIN: One would like to know about the physical examination. Diffuse tenderness was described. In a person as sick as this it is frequently difficult to determine more than the fact that the patient merely reacts to abdominal pressure, but no more in one area than in another.

One would like to know about the presence of microscopic blood in the stool; a guaiac-positive reaction would perhaps aid in making the diagnosis. Was an abdominal tap done? The presence of blood in the fluid removed by the passage of a small-lumen needle into the abdominal cavity is quite significant; a negative examination is of no value.

DR. CRYSTAL: The stools were guaiac negative. An abdominal tap was not done.

DR. HAMLIN: From the description of the physical examination one would be justified in drawing the conclusion that there was widespread peritoneal irritation. Diffuse tenderness is certainly suggestive, because in simple obstruction, unless the vomiting itself produces enough muscle tenderness, localization is usually rather narrow. It is perhaps unwise, however, to draw any conclusion as to that. Certainly the laboratory examinations do not add to the picture; in an elderly dehydrated patient the white-cell count is frequently increased, even more than this.

I am not at all clear whether or not this woman had peritonitis. I am inclined to say that she at least had peritoneal irritation.

We now come down to the origin of the intestinal obstruction, the aforementioned red herrings being present. The first and most obvious one is the tender, irreducible lump in the left groin. Were this the site of an incarcerated hernia causing obstruction with the period of time that had elapsed, — forty-eight hours, — one would expect strangulation to have occurred. One would also expect the patient to complain of pain in that particular area rather than of generalized abdominal cramps. Also since it is so obvious, I am inclined, on the basis of what generally turns up at these meetings, to discard it, at least temporarily.

Then we have the lovely red herring in the x-ray film — a 4-cm. spheroid mass containing calcium. at which point it appears that the dilated bowel stops. That is interesting indeed. We have a history of an attack twenty-five years previously, which is consistent with gall-bladder disease. The patient had an aversion to fatty and fried foods, which is also consistent with gall-bladder disease, and it is perfectly possible that she had, over a long period of time, gradually eroded away an adhesion between the gall bladder and the small bowel and passed a stone into the small intestine, where it lodged and

produced the obstruction. It is present on every film, but as Dr. Schulz has pointed out, it might also have been due to a calcified fibroid.

What are the other possibilities of small-bowel obstruction? At this patient's age, with the obvious heart condition that she had, — hypertension for a long period of time, — one must consider vascular occlusion in the mesentery of the small bowel, either embolism or thrombosis. If one tried to fit that into the story as given, I believe that it would be easier to ascribe the accident to thrombosis than to embolism. Although the onset was sudden, one gets the impression that she gradually became worse and that the degree of illness on entry was more attributable to the electrolyte imbalance and loss of fluids in general than to anything else.

There are a number of other things that can produce this picture, — volvulus, tumor and adhesions, — but I do not believe that we have to consider them as closely as the first three that I have mentioned, namely, hernia, gallstone ileus and vascular accident. There are many things against a vascular accident: the patient did not complain of pain in the back, she had a negative guaiac test on the stool, and there was no other evidence of blood. I eliminate the hernia on the basis of lack of marked tenderness. Was any history obtained regarding a change in the appearance of this mass in the left groin?

DR. CRYSTAL: There was no change in appearance. She said that it was more tender in the region of the hernia than it had been before the onset.

DR. HAMLIN: That does not help.

I must stick to one thing, and since the apparent gallstone appeals to me, I am going to call this gallstone ileus. I am sure that the surgeon hoped that that was the diagnosis. It is a relatively infrequent condition, and a rather satisfactory one to operate on.

DR. CHESTER M. JONES: Where is the gallstone in gallstone ileus usually found?

DR. HAMLIN: Usually in the lower third of the ileum. Here, it could be close to the terminal ileum. From the story and certain deductions that can be drawn from the films it appears that the major part of the small bowel was affected by the obstruction.

#### CLINICAL DIAGNOSIS

Gallstone ileus?

Incarcerated femoral hernia?

#### DR. HAMLIN'S DIAGNOSIS

Gallstone ileus.

#### ANATOMICAL DIAGNOSIS

Gallstone ileus.

#### PATHOLOGICAL DISCUSSION

DR. CRYSTAL: We thought that the condition was either a gallstone ileus or an incarcerated hernia. If the former, we considered that operation was contraindicated because of the duration and the patient's age. We did think, however, that it was



worthwhile to subject her to a less serious procedure and gambled on the hernia. She had a hernia, which was incarcerated but not strangulated, with viable omentum. We later operated and found that she had a gallstone of about the expected size. The bowel had no necrosis around it. It was only necessary to make a slit over the stone, deliver it and close the bowel. It was an extremely gratifying operation.

DR. BENJAMIN CASTLEMAN: How far was the tip of the Miller-Abbott tube from the stone?

DR. CRYSTAL: It was within 15 or 20 cm.

DR. HAMLIN: So the stone held tightly.

DR. CRYSTAL: Apparently not, and for that reason we did not use the maneuver of moving the stone back several centimeters rather than cutting into area that had undergone damage. Since the bowel

was in good condition there appeared to be no indication for moving the stone.

DR. CASTLEMAN: The operation is a lot easier with the Miller-Abbott tube in place?

DR. HAMLIN: A word might be said about that. In the article that I have previously mentioned, Dr. McKittrick points out that the danger of operation on simple obstruction, without obvious strangulation but with distention of the bowel, is much greater than taking the chance that there may be strangulation and resultant perforation; delay in order to deflate the bowel with a Miller-Abbott tube in obstruction over twenty-four hours old is almost mandatory.

DR. CASTLEMAN: That is the point I wanted to bring out.

**Correction.** Perusal of the published record of Case 30521, which appeared in the December 28, 1944, issue of the *Journal*, made me suddenly

plicating posterior myocardial infarction or a complicating acute cor pulmonale, or both, superimposed on a myocardial infarction that was obvious both

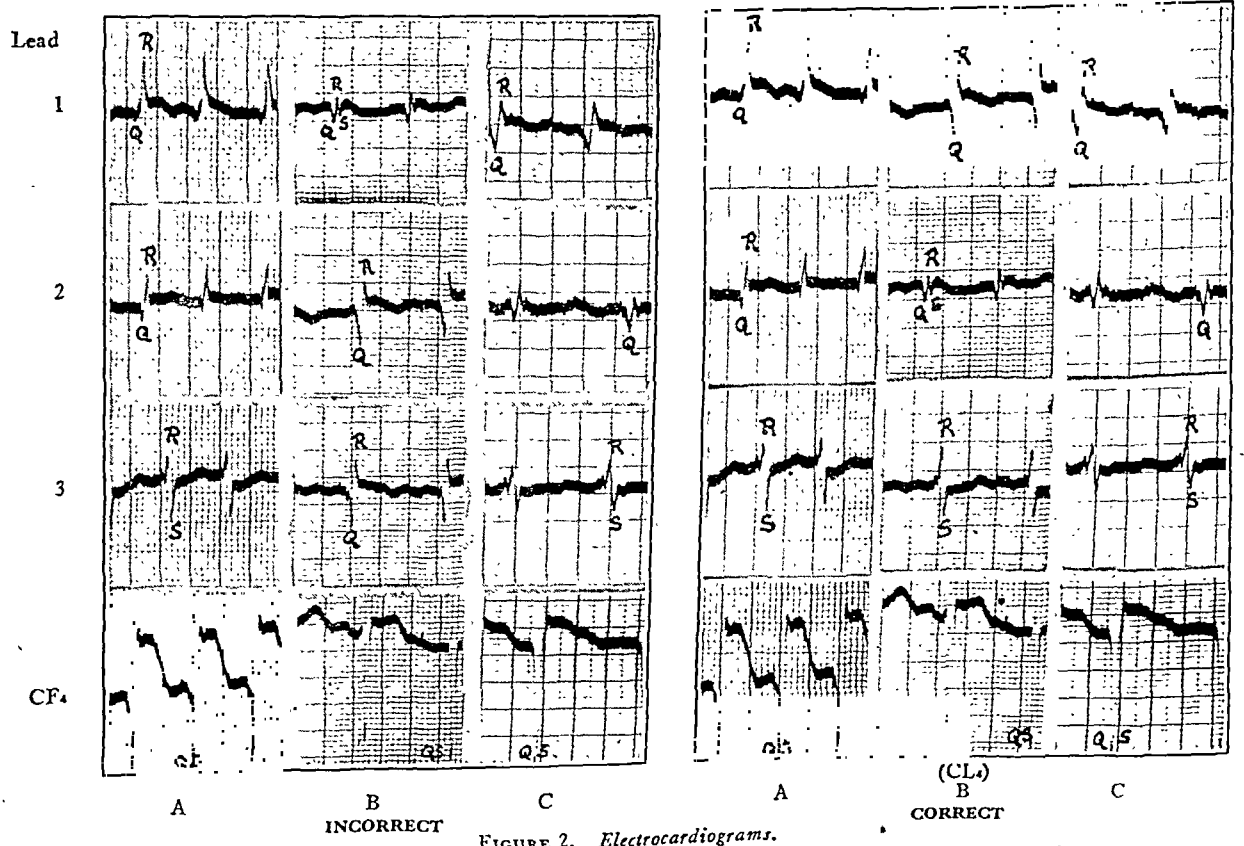


FIGURE 2. Electrocardiograms. A was taken on the day of admission; B, on the third hospital day; and C, on the fifth hospital day.

aware of an error in Figure 2, which presented three electrocardiograms taken, respectively, on the day of admission, on the third hospital day and on the fifth hospital day. As had been noted in the protocol of the case and in my own discussion, there was a striking difference between the second electrocardiogram and the first and third tracings. This had, at first, seemed to fit the possibility of a com-

by history and electrocardiogram and was evidently anterior in position. There was no posterior myocardial infarction found at autopsy, however, and a possible cor pulmonale resulting from a complete obstruction by an interauricular thrombosis of the right pulmonary veins as they entered the left auricle, and gross infarction of the right lung, should have been apparent at the time of admission, when

x-ray evidence of massive involvement of the right lung was already clear. Thus, the confusing change in the electrocardiogram was difficult to explain on the basis of both the clinical and the post-mortem findings.

A closer inspection of the electrocardiographic records revealed at once the probable error that had crept in to cause this confusion. A glance at Figure 2 as published and Figure 2 as corrected, both of which are presented herewith, shows the probability, in fact almost certainty, that in the strip (B) taken on the third hospital day, the original Lead 1 should have been labeled Lead 2, that Lead 2 should have been labeled Lead 1 and that Lead 3 is upside down. This can readily be accounted for by the transposition of the left-arm and left-leg wires, which is less frequent and also more easily overlooked than the error of transposing the arm wires, which results in an inversion of Lead 1, with a switch of Leads 2 and 3. Also, of course, in this record, Lead CF<sub>4</sub> becomes Lead CL<sub>4</sub>, since it was the left arm, and not the left leg, that was connected with the chest electrode.

The error in the precordial lead is slight, but that in the limb leads becomes extremely significant.

There is no longer a Q wave in Lead 3 and only a small Q wave in Lead 2, whereas the prominent Q wave in Lead 1, also found in the next electrocardiogram, is perfectly consistent with a gross anterior myocardial infarct, as is also the inversion of the T wave in that lead. Although there was no observation at the time of taking this record of the error in the placing of the lead wires, the fact that the electrocardiogram was not taken in the routine work of the Cardiac Laboratory, as well as the confusing picture that resulted and has been explained above, makes it quite certain that an error of technic was responsible for what had seemed like a curious and complicated picture in the electrocardiographic pattern. Thus, the second paragraph of my own discussion of this case, found on page 888, can be completely omitted, with but slight revision of the first paragraph.

Finally, this error and the necessary correction are another example of the constant need of everlasting vigilance in the interpretation of electrocardiograms; one should be particularly on the lookout for the very errors in technic that occurred here. We ourselves have constantly preached about this and yet have here been guilty of the same offense.

PAUL D. WHITE.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

## POSTWAR PLANNING

IN an editorial carried in the August 31 issue, the *Journal* visualized "a postgraduate medical education program of unprecedented proportions—something that will have to bring into use a larger proportion of clinical material than has ever before been utilized." Under the date of November 9, the Committee on Medical Education and Hospitals of the American Medical Association has addressed a request for information to all hospitals approved for internship and residency, enclosing a copy of a recent report,\* in which it was shown that "opportunities for graduate training in surgery, obstetrics-gynecology, otolaryngology and ophthalmology will

\*Johnson, V., and Arestad, F. H. Educational facilities required for returning medical officers. *J. A. M. A.* 126:253-257, 1944.

probably need to be doubled in number while facilities in urology, internal medicine, orthopedics, pediatrics, pathology, radiology, psychiatry and neurology may require an increase of 30 to 70 per cent."

It is conceivable that these increased opportunities may be devised, as and when the war ceases to preoccupy many of the most vigorous and educationally effective members of the profession, thus permitting them to return to peacetime bedsides and operating rooms. Until this is possible, however, it is unrealistic to expect any great expansion of teaching activity. In the request for information referred to above it is stated that training courses in industrial medicine and general medicine will be called for. These are large subjects, having more in common with general practice than they do with the orthodox type of specialty, and they should be made as attractive as possible, since the relative distribution of workers in special and general fields needs sharp adjustment if the people are to be most advantageously served in the future. Up to 1944, for example, more otolaryngologists than internists had been certified and there were nearly as many radiologists as there were surgeons.

In the report, particular attention is called to the fact that there is a major time discrepancy between the courses now available and those that it is estimated will be demanded. Thus, over 90 per cent of the opportunities for postgraduate training in 1943-1944 were in courses of about one month's duration, whereas it is estimated that only 7 per cent of the postwar demand will be for such short courses. How can these longer courses be organized? Here, in prospect, are some thousands of candidates for training—training that will require a greater number of residencies than are now in or readily put into commission on a modern basis. These candidates will tend to compete with one another for the better opportunities, and this competition will, in turn, tend to make of the opportunities themselves a marketable commodity. There is therefore a real need for some sort of supervision by recognized and competent authorities, such as the American Medical Association, the surgeons general of the United States Army, Navy and Public Health Service, the American and the Catholic

hospital associations, the American colleges of Surgeons and of Physicians, the boards in the medical specialties, the medical schools, the state licensing boards and medical societies, the Veterans Administration and perhaps many other interested groups. It is good to know that the Massachusetts Medical Society now has a Postwar Planning Committee actively studying the means by which it may be of help in this great task.

### DIABETES — A NEGLECTED DISEASE — AND WHAT SHOULD BE DONE ABOUT IT

DIABETES is a neglected disease when compared with tuberculosis or infantile paralysis. Diabetic patients equal in number those with tuberculosis and are four times as numerous as those crippled with infantile paralysis. Yet, contrast the organizations devoted to the control and eradication of tuberculosis throughout the United States and the huge sums raised to combat the disease, as well as the \$11,000,000 or more collected for the study and care of cases of infantile paralysis, with the one small national and the four recently created local organizations devoted to diabetes.

The need for an aroused interest in diabetes is growing, because each year the number so afflicted is sure to increase. It is a disease of middle adult life, and the population of the country is steadily advancing to that decade, forty-five to fifty-five years, in which the onset of diabetes is most frequent. Diabetic patients themselves are contributing to the gain in numbers because they are living, on the average, three times as long as they did before the introduction of insulin. Furthermore, increased medical supervision and improved vital statistics are revealing more cases.

Notwithstanding the availability of insulin, many patients still die needlessly of diabetic coma. This could be remedied in a large degree if each hospital in the country would plan and equip itself for the efficient treatment of diabetic emergencies. The time required and the capital involved for equipment would be minimal, and the costs for available

services of laboratory personnel at night and on Saturday afternoons, Sundays and holidays would be insignificant compared with that incurred for maintaining operating rooms during those same periods. Indeed, a hospital that does not exercise such foresight in the not distant future may be held derelict to its local needs.

The discovery of alloxan diabetes has opened up opportunities for research never before even dreamed of, and these new pathways of investigation should be exploited. Already, in less than a year and a half following the report of Shaw Dunn's original work, the results of experiments with alloxan have been published from eight different countries.

*To treat the rapidly growing number of diabetic patients, to protect them in their emergencies and complications and to foster research, funds are needed, and the most readily available source is from the patients themselves. They constitute an intelligent group and are able and ready to contribute if asked. They are not content with the present methods of treatment. They know that research gave them insulin, and they want to provide for more research to improve present methods of treatment. They are painfully aware of the shortage of hospital beds, not simply for routine care but even for the serious complication of the disease. They appreciate that fellow patients are dying needlessly of diabetic coma because of their lack of a diabetic education or because of inferior medical treatment. They know that diabetes is hereditary, and they wish to protect their families, just as their relatives wish to avoid diabetes. All diabetic patients and their relatives in any community should be asked to furnish the funds for facilities in their local hospital to protect them in emergencies and to promote research in hospitals that are properly qualified. They rightly look on such gifts as personal insurance.*

Physicians in the United States should raise \$10,000,000 in 1945 for the creation of diabetic funds and for the betterment of hospital facilities. If this is not done, they, too, can be held derelict, because patients and their relatives are more than ready to give the money to improve the care of the diabetic patient.

## MASSACHUSETTS MEDICAL SOCIETY

The *Journal* lacks extra copies of the January 13, April 6, May 11, June 1 and July 27, 1944, issues. Many requests have been made by libraries and other subscribers who wish to bind Volumes 230 and 231 but who did not receive those particular issues. If any subscribers who do not bind their copies have the above-mentioned issues on hand, the *Journal* will gladly pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15).

MASSACHUSETTS DEPARTMENT  
OF PUBLIC HEALTHDEFIBRINATED HORSE BLOOD  
FOR LABORATORY USE

For a good many years the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Public Health has been furnishing defibrinated horse blood to various laboratories in the Boston area. As with other products, this has been a free service. In the past, the service has been limited to those who could have the blood picked up by messenger, since no evidence was available that the blood would withstand shipment by mail at all seasons.

Recently there has been an increased demand from hospitals and laboratories in other parts of the Commonwealth for this service. During the past summer a supply of such blood has been mailed to several such laboratories with gratifying results. The blood has arrived in good condition and has obviated the need for bleeding a person or animal for a few red cells every time a batch of culture medium is prepared.

It is now planned to make this service available to all the hospitals and laboratories of the Commonwealth. The requirements are that such institutions return promptly the empty containers for further use and that they gauge their needs so that a minimum of blood will be wasted. Hospitals and laboratories that are placed on the mailing list may receive up to 200 cc. of defibrinated blood at intervals of two weeks. This will ensure a continuous supply of usable blood, since it can be kept in satisfactory condition for this period if properly refrigerated.

Inquiries should be addressed to the Antitoxin and Vaccine Laboratory, 375 South Street, Jamaica Plain 30, attention of Dr. J. A. McComb.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Textbook of Gynecology.* By Emil Novak, M.D., associate in gynecology, Johns Hopkins University School of Medicine, and gynecologist, Bon Secours and St. Agnes hospitals, Baltimore. Second edition. 8°, cloth, 708 pp., with 456 illustrations. Baltimore: William and Wilkins Company, 1944. \$8.00.

This second edition of a textbook first published in 1941 has been thoroughly revised and brought up to date, which necessitated a complete resetting of the text. Many new original illustrations, including a considerable group of color photographs, have been added. Two new chapters, covering the embryology of the female generative organs and the female urologic conditions that are of special interest to the gynecologist, are included. The work has been written primarily for students and general practitioners, and for this reason details of operative technic have been omitted.

*An Introduction to Public Health.* By Harry S. Mustard, M.D., LL.D., director and professor of public health practice, Delamar Institute of Public Health, College of Physicians and Surgeons, Columbia University, New York City. Second edition. 8°, cloth, 283 pp. New York: Macmillan Company, 1944. \$3.25.

The first edition of this manual was written in 1935, and this new edition has been completely revised and brought into conformity with modern practice in the public-health field. Two chapters, one on industrial hygiene and the other on medical care, have been added, and the morbidity and mortality data reflect the latest available statistics. The volume is designed for use in all introductory courses in public health whether in schools of public health, in medical schools, in nursing schools or in colleges.

*Our Concern — Every Child: State and community planning for wartime and postwar security of children.* By Emma O. Lundberg. Children's Bureau, Publication 303. 8°, paper, 84 pp. Washington: Government Printing Office, 1944. 15 cents.

This pamphlet discusses in an abbreviated form the welfare of children in peace and in war from the viewpoints of both the state and the community. It provides outlines for planning services in all their aspects for the welfare of children.

*Malaria: Its diagnosis, treatment and prophylaxis.* By William N. Bispham, M.D. 8°, cloth, 197 pp., with 4 plates and frontispiece. Baltimore: Williams and Wilkins Company, 1944. \$3.50.

This small book has been written to give the physician a knowledge of the clinical features of malaria. It considers etiology, symptomatology, diagnosis, pathology, treatment, prevention and immunity. Blackwater fever is briefly discussed. The final chapter is on prevention and treatment of malaria in West Africa and is contributed by Dr. L. T. Coggeshall. The first two chapters comprise a short history of malaria and its geographic distribution. A good index makes all material available, and this manual should be useful as a reference source.

*Plaster of Paris Technic.* By Edwin O. Geckeler, M.D., associate professor of orthopedic surgery and chief of the Fracture Service, Hahnemann Medical College and Hospital, Philadelphia. 8°, cloth, 220 pp., with 208 illustrations. Baltimore: Williams and Wilkins Company, 1944. \$3.00.

Unusually well illustrated and suitable for the instruction of graduate and undergraduate students, the text gives a

practical working knowledge of the everyday conditions in which plaster of Paris may be used. There are special chapters on its use in war surgery and in the treatment of burns.

*Strophanthin: Clinical and experimental experiences of the past twenty-five years.* By Bruno Kisch, M.D. 8°, cloth, 158 pp., with 24 illustrations. New York: Brooklyn Medical Press, 1944. \$4.00.

This monograph has been written for the purpose of urging the American medical profession to reconsider the question of the clinical application of strophanthin. In his text the author embodies conclusions derived from a number of experiments on animals and records his clinical observations, particularly those on how the drug affects the vagus nerve and on how the extrasystoles should be judged after strophanthin administration. A comprehensive review of the literature of the past twenty-five years has been appended to the text. The book is well printed, with a good type on good paper.

*The Blood Pressure and Its Disorders including Angina Pectoris.* By John Plesch, M.D. (Budapest), M.D. (Berlin), L.R.C.P. and S. (Edin. and Glas.). 8°, cloth, 149 pp., with 61 illustrations. Baltimore: Williams and Wilkins Company, 1944. \$4.50.

This small manual discusses arterial and venous blood pressures, with particular reference to angina pectoris.

*Fertility in Women: Causes, diagnosis and treatment of impaired fertility.* By Samuel L. Siegler, M.D., attending obstetrician and gynecologist, Brooklyn Women's Hospital, attending gynecologist, Unity Hospital, assistant obstetrician and gynecologist, Greenpoint Hospital, and consultant in gynecology, Rockaway Beach Hospital. With a foreword by Robert L. Dickinson, M.D. 8°, cloth, 450 pp., with 194 illustrations. Philadelphia: J. B. Lippincott Company, 1944. \$4.50.

The various aspects of abnormal and impaired fertility are discussed from a systemic or functional point of view. There is a long chapter on the physiology of the female sex cycle and the various methods for evaluating its efficiency. Considerable space is devoted to both general and specific therapy, to the treatment of ovarian imbalance and to the faulty reception of spermatozoa.

*Manual of Psychological Medicine for Practitioners and Students.* By A. F. Tredgold, M.D., F.R.C.P., F.R.S.E., consulting physician, University College Hospital, London, and lecturer on mental deficiency, London University. 8°, cloth, 298 pp. Baltimore: Williams and Wilkins Company, 1945. \$5.00.

This small book is essentially a manual on disorders of the mind for the use of all those who are brought into contact with military personnel.

*The Diseases of the Endocrine Glands.* By Herman Zondek, M.D. (Berlin), director of the Medical Division, Bikur Cholim Hospital, Jerusalem. Translated by Carl Prausnitz Giles, M.D. (Breslau), M.R.C.S. (Eng.), L.R.C.P. (Lond.). Fourth (second English) edition. 8°, cloth, 496 pp., with 180 illustrations. Baltimore: Williams and Wilkins Company, 1944. \$11.00.

The first edition of this book was written in 1935, and the present edition has been revised to embody important results of recent researches.

*Manual of Military Neuropsychiatry.* Edited by Harry C. Solomon, M.D., professor of psychiatry, Harvard Medical School, and medical director, Boston Psychopathic Hospital;

and Paul I. Yakovlev, M.D., clinical director, Walter E. Fernald State School, and instructor of neurology, Harvard Medical School. 12°, cloth, 746 pp., with 15 illustrations. Philadelphia and London: W. B. Saunders Company, 1944. \$6.00.

This manual is intended as a reference text on topics of clinical neurology and psychiatry and has been prepared especially for medical officers, often remote from libraries and textbooks. The book is divided into six parts: history of neuropsychiatry during World War I and general organization during the current war; induction (having to do with the screening and examination of inductees); administration and disposition; clinical entities; prophylaxis and therapy; and special topics.

*Secretory Mechanism of the Digestive Glands.* By B. P. Babkin, M.D., D.Sc., LL.D., research professor of physiology, McGill University, Montreal. 8°, cloth, 900 pp., with 220 illustrations. New York: Paul B. Hoeber, Incorporated, 1944. \$12.75.

This new book on the physiology of the digestive glands embodies the work performed by the author and his co-workers during the last fourteen years in the Department of Physiology of McGill University. It is not monographic in scope, since no attempt has been made to review the whole of the literature concerned with the secretory function of all the digestive glands. The book deals mainly with the mechanisms regulating secretory activity, as exemplified in particular by the functions of the gastric, salivary and pancreatic glands. So far as possible, the author has included in his work the more important facts known in regard to the secretory functions of the digestive tracts up to the present date. An extensive bibliography is appended to the text.

*The Radiology of Bones and Joints.* By James F. Brailsford, M.D., Ph.D., F.R.C.P., F.I.C.S., Hunterian professor, Royal College of Surgeons, England (1934-1935 and 1943-1944), radiological demonstrator in living anatomy, University of Birmingham, radiologist to St. Chad's Hospital, the City of Birmingham Infant Welfare Centres and the Military Hospital, Hollymoor, Birmingham, and consulting radiologist to the City of Birmingham Hospitals, the Robert Jones and Agnes Hunt Orthopaedic Hospital, the Birmingham Accident Hospital and Rehabilitation Centre and the Birmingham Mental Hospital. Third edition. 8°, cloth, 440 pp., with 404 illustrations. Baltimore: Williams and Wilkins Company, 1944. \$12.00.

Ten years have elapsed since the publication of the second edition of this special work, first published in 1934. The book now represents an analysis of the work of the author during the past twenty-five years. The present edition gives a more comprehensive account of the variations of the normal developmental and the pathologic conditions in bones and joints than was possible in the earlier editions. Particular attention has been paid to the changes in bones and joints resulting from trauma, the osseous dystrophies, tuberculosis, syphilis and neoplasms. The treatment of certain conditions has been considered in the light of radiographic findings. An extensive bibliography is appended to the text. The type and paper are good, and there are many full-page radiographic plates.

*Diseases of the Digestive System.* Edited by Sidney A. Portis, M.D., associate professor of medicine, University of Illinois (Rush) Medical School, attending physician, Michael Reese Hospital, consulting physician, Cook County Hospital, and

consultant in medicine, Institute of Psychoanalysis, Chicago. 8°, cloth, 932 pp., with 182 illustrations. Philadelphia: Lea and Febiger, 1944. \$11.00.

This second edition of an authoritative work by fifty contributors has been completely revised and reorganized to meet the needs of students and teachers in the field. Special emphasis has been placed on the psychosomatic aspects of gastrointestinal symptoms. The chapters have been rearranged, placing the physiology of each organ before its clinical discussion. Each contributor has considered the effects of emotional stimuli on the gastrointestinal tract. The chapter on psychosomatic disturbances has been enlarged. Selected references have been appended to each chapter.

*Recent Advances in Anaesthesia and Analgesia, including Oxygen Therapy.* By C. Langdon Hewer, M.B., B.S. (Lond.), D.A. (Eng.), senior anaesthetist, St. Bartholomew's Hospital and St. Andrew's Hospital, Dollis Hill, anaesthetist, Brompton Chest Hospital and Emergency Medical Service, and consulting anaesthetist, Mid-Herts and West-Herts hospitals. Fifth edition. 8°, cloth, 343 pp., with 141 illustrations. Philadelphia: Blakiston Company, 1944. \$5.50.

In this edition it has been possible to include new material on a large number of important subjects. Each section has been carefully revised throughout, and attention has been given to the military aspects of anesthesia. An additional chapter on anesthetic charts and records has been placed at the end of the book. To each chapter has been appended a selected list of references.

*The Urinary Tract: A handbook of roentgen diagnosis.* By H. Dabney Kerr, M.D., professor of radiology, State University of Iowa College of Medicine; and Carl L. Gillies, M.D., associate professor of radiology, State University of Iowa College of Medicine. 8°, cloth, 320 pp., with 120 illustrations. Chicago: Year Book Publishers, Incorporated, 1944. \$5.50.

The objective of this small handbook is to provide student, practitioner, urologist and radiologist with selected plates of the commoner and some of the uncommon lesions of the urinary tract. The plates are of cases studied radiographically at the University of Iowa hospitals. All reproductions show the structures at about a third of the actual size, and no retouching has been done on the negatives. In every case illustrating pathologic involvement, the hospital record of the patient has been examined and the diagnosis has been based to a large extent on the study of all available information. Whenever possible, several examples of each condition have been included, because of the fact that no two normal structures or no two lesions appear exactly alike. The text is divided arbitrarily into sections on the kidneys, ureter, bladder and urethra.

*Freud's Contribution to Psychiatry.* By A. A. Brill, Ph.B., M.D. 12°, cloth, 244 pp. New York: W. W. Norton and Company, Incorporated, 1944. \$2.75.

The author presents an intimate evaluation of the development of psychoanalysis as he himself lived through it, emphasizing the statements with appropriate quotations from his extensive correspondence with Freud. Dr. Brill was one of the pioneers of psychoanalysis and since 1907 has devoted

all his time to the study and dissemination of Freud's teachings. He was Freud's first English translator, his most active expositor in this country and his most ardent co-worker and close friend.

*Foster Home Care for Mental Patients.* By Hester B. Crutcher, director of social work, State of New York Department of Mental Hygiene. 8°, cloth, 199 pp. New York: The Commonwealth Fund, 1944. \$2.00.

The author discusses the meaning and the objectives of family care, its development in the United States and foreign countries, some of the results achieved, the financial as well as the therapeutic advantages, various procedures, including selection and supervision of cases, and forms for keeping the necessary records. Foster-family care is care under hospital supervision of mentally ill persons or mental defectives in families other than their own. It is not mere custody but therapeutic care under the supervision of the mental hospital. It is a recent development in the United States.

*The Medical Clinics of North America.* Boston Number: September, 1944. 8°, cloth, 263 pp., illustrated. Philadelphia: W. B. Saunders Company, 1944. \$3.00.

## NOTICES

### NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, March 1, in the classroom of the Nurses' Residence at 7:15 p.m. The topic will be "Selection of Hypertensive Patient for Sympathectomy." Dr. Dera Kinsey will be chairman.

### JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a.m.

#### MEDICAL CONFERENCE PROGRAM

- Friday, March 2 — The Significance of the Eosinophil Count in Acute Infections. Dr. Francis C. Lowell.
- Wednesday, March 7 — Dental Medicine. Dr. Robert W. Buck.
- Friday, March 9 — Protein Nutrition in Problems of Medical Interest. Dr. Fredrick J. Stare.
- Wednesday, March 14 — The Glaucoma Problem and General Medicine. Dr. Joseph Igersheimer.
- Friday, March 16 — Protolytic Enzymes in Tissues. Dr. Paul C. Zamecnik.
- Wednesday, March 21 — The Diagnosis of Diabetes Mellitus. Dr. Joseph Rosenthal.
- Friday, March 23 — Some Aspects of Cardiac Surgery. Dr. Robert E. Gross.
- Wednesday, March 28 — The Surgical Gallbladder. Dr. Leland S. McKittrick.
- Friday, March 30 — Graphic Methods and Auscultation of the Heart. Dr. Aldo A. Luisada.

On Monday mornings (except March 12) clinics will be given by Dr. Samuel Proger. On Tuesday and Thursday mornings Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings clinics will be given by Dr. William Dameshek.

(Notices continued on page xvii)

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## SEVENTY-FIVE YEARS OF PUBLIC HEALTH IN MASSACHUSETTS

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BOSTON

THE seventy-fifth anniversary of the founding of the State Board of Health of Massachusetts calls to mind certain outstanding personalities and their relation to the development of public-health theory and practice in the Commonwealth. Most of these — though not all — were medical men; some of them were distinguished as well in fields other than that of public health. It is the purpose of this article to trace the origin and development of the public-health movement in Massachusetts and to discuss the part played by outstanding men who guided it through the years since 1869.

### LEMUEL SHATTUCK, PIONEER

The first to appear on the public-health horizon in this state, of those whose impress was an indelible one, was Lemuel Shattuck. Although bearing a name now famous for its medical connotations, Shattuck was not medically trained, but was first a schoolteacher and later a publisher and bookseller. He early became interested in subjects that are now generally included in the scope of public health. He it was who broke the ground and sowed the seed that many years later produced the first permanent state board of health in America. Shattuck began by obtaining the passage of an act on which is based the present system of birth and death registration in this state. In 1849, he helped to secure the passage of legislation providing for a sanitary survey of the Commonwealth and served as a member of the commission appointed for that purpose. The report of the commission appeared in 1850 and is an extraordinary document, even today, in the light of seventy-five years of rapidly increasing knowledge and experience. The caliber of the thinking exhibited in it may be gathered from the following quotation:

We believe that the conditions of perfect health, either public or personal, are seldom or never attained, though attainable; that the average length of human life may be very much extended, and its physical power greatly augmented; that in every year, within this commonwealth, thousands of lives are lost which might have been saved; that tens of thousands of cases of sickness occur which

might have been prevented; that a vast amount of unnecessarily impaired health and physical debility exists among those not actually confined by sickness; that these preventable evils require an enormous expenditure and loss of money, and impose upon the people unnumbered and immeasurable calamities, pecuniary, social, physical, mental and moral, which might be avoided; that means exist, within our reach, for their mitigation or removal; and that measures for prevention will effect infinitely more than remedies for the cure of disease.

Nearly all the general aspects of present-day health practice are at least foreshadowed in the Shattuck report. As a sampling of the quality and scope of the committee's recommendations one may refer to these: the establishment of a general board of health; increasing the number of effective local boards of health; census of the population; registration of births, marriages and deaths; sanitary surveys; study of sickness in schools; tenements for the laboring classes; quarantine regulations; periodical and special vaccinations; abatement of the smoke nuisance; and many others, some of which have not even yet received adequate attention.

### HENRY I. BOWDITCH, ORGANIZER

A period of twenty years followed the presentation of this report, during which the Legislature did nothing to further the objectives of the Shattuck report. Another outstanding figure then appeared in the person of Henry Ingersoll Bowditch. Dr. Bowditch, after graduating from Harvard Medical School in 1832, studied in France under the famous Louis. A characteristic of the latter was his insistence on statistical proof as an aid in estimating the value of the various forms of medical treatment. It is perhaps not too farfetched to suppose that this kind of training influenced Bowditch in his later devotion to the cause of public health in Massachusetts. Bowditch had an independent mind and was not afraid to propose new measures even in the face of disapproval on the part of medical colleagues. He was a man of standing and influence at the time when the State Board of Health was established; he was known for his work on tuberculosis, and had been professor of clinical medicine at Harvard Medical School.

\*Formerly Director, Division of Hygiene, Massachusetts Department of Public Health.



As a result of energetic effort on the part of Dr. Bowditch and like-minded people and, it is said, because of an outbreak of typhoid fever that aroused fear in the minds of certain legislators, Lemuel Shattuck's project at last took form, and a state board of health was created by act of the Legislature in 1869. Dr. Bowditch was chosen chairman of this board. The statute that started the new board on its long and honorable course has often been quoted but will bear repetition. It reads as follows:

The Board shall take cognizance of the interests of the life and health of the citizens of this commonwealth. They shall make sanitary investigations and inquiries in respect to the causes of disease, and especially of epidemics and the sources of mortality, and the effects of localities, employments, conditions and circumstances upon the public health; and they shall gather such information in respect to those matters as they may deem proper for diffusion among the people. They shall advise the government in regard to the location and other sanitary conditions of any public institutions, and shall report to the Legislature each year with such suggestions as to legislative acts as they deem necessary.

For ten years, Bowditch remained the main-spring of the State Board of Health, ably seconded by two secretaries of the Board, Dr. George Derby, who died in office in 1874, and his successor, Dr. C. F. Folsom. These ten years were years of real pioneering in the virgin field of public health. The activities of this period have been well summarized by Whipple<sup>1</sup> in these words:

The Massachusetts State Board of Health was studying Massachusetts, her people and their health, the diseases common among them, the sanitation of their homes, the nuisances to which they were subjected, the water they drank, the method of waste disposal, the ventilation of their school houses, the disposal of their dead. The Board was "taking cognizance of the interests of health and life."

#### STRANGE INTERLUDE

In 1879, politics reared its ugly head. General Ben Butler was fulminating against what he termed the numerous commissions that were "spending wastefully the people's money." Those in charge of the government at that time thought to avoid trouble by a little appeasement. The State Board of Health was merged and at least partly submerged in the State Board of Health, Lunacy and Charity. Dr. Bowditch soon resigned in protest.

In the midst of the tribulations of the triple-headed board, a new figure appeared as a worthy successor to Dr. Bowditch. This was Dr. Henry Pickering Walcott, who was later to reach the stature of "a great sanitary statesman." Dr. Walcott joined the Board of Health, Lunacy and Charity in 1880 as executive for its health committee. Two years later he resigned this position to become chairman of the committee. He remained in charge of the State's health activities for thirty-two years.

#### HENRY P. WALCOTT, SANITARY STATESMAN

It is hard to appraise the full value of the work of a man like Henry P. Walcott. Always an austere

and dominant personality, he nonetheless was able to work with other strong men. A noteworthy example of this was his long association with the engineer, Hiram F. Mills, who shared with Walcott much of the credit for the Board's accomplishments during twenty-eight years, the services of both men ending with the reorganization of the Board in 1914.

It seems, in retrospect, as though Dr. Walcott's strength lay in an ability to take a broad view of the whole field of public health, to appreciate the value of new discoveries and to keep clearly in mind the proper relations of state to local communities. During his long administration occurred some of the great advances in public-health knowledge. These were at once absorbed by the Massachusetts State Board of Health and put to work. Many of these contributions to knowledge originated with the state organization itself. An example of this at once comes to mind in the research work of the Lawrence Experiment Station and the construction of the Metropolitan Water and Sewerage systems.

The Lawrence Experiment Station was planned by Mills in 1887 and represented a great advance in the possibilities of the sanitary control of the environment. It has been said, "The investigations at the Lawrence Experiment Station laid the foundation for the scientific treatment of sewage and have given the initiative for similar investigations in this and other countries."<sup>2</sup> In 1893, a sand-filtration plant for the purification of the water supply of the city of Lawrence was built after plans by Mills. The saving of lives brought about as a result of these and similar engineering accomplishments can hardly be overestimated. The period covered by the life of the State Board of Health from 1869 to 1914 may truly be called the era of sanitary engineering, and of this era two of the outstanding promoters were Walcott and Mills.

There were other well-known figures as well whose work centered in the State Board of Health during that period. Only passing reference can be made to them here. The first in point of time was Dr. Samuel Abbott, secretary of the Board from 1886 to his death in 1904. His report "Vital Statistics in Massachusetts from 1856 to 1895" was a striking piece of work. It may be found in the 1896 report of the Board. The second, Dr. Theobald Smith, had, of course, an international reputation quite apart from his services with the Board. He came to Massachusetts in 1895 as director of the recently established Antitoxin Laboratory. The production and distribution of diphtheria antitoxin represented a new service to Massachusetts physicians and their patients — a type of service that has been steadily extended since then. The Bacteriological Laboratory, too, starting at that time modestly under the State Board of Health, has, through the devoted service of its present chief and her associates, become indispensable to thousands of physicians throughout the Commonwealth. The

Wassermann Laboratory, although established later, in 1915, should be referred to here. It also has grown amazingly in activities and usefulness.

Dr. Smith resigned the directorship of the Antitoxin Laboratory in 1914 and was succeeded by Dr. Milton J. Rosenau, whose great reputation, like that of Dr. Smith, came from research, teaching and writing. Dr. Rosenau held the directorship until 1920.

Before turning from the State Board of Health to its successor, two other secretaries of the Board must be mentioned. Dr. Charles Harrington served from 1905 to 1909, at the same time serving as professor of hygiene at Harvard Medical School. He was succeeded by Dr. Mark Richardson, who ably carried on the work until the Board was reorganized in 1914.

### THE DEPARTMENT OF HEALTH

The year 1914 marks a great change in state health administration in Massachusetts. The State Board of Health had done a magnificent piece of work with the older type of setup, but a different kind of administrative plan was beginning to be popular. Instead of unpaid boards with paid secretaries, states were turning to a single-headed department, with a full-time commissioner and a part-time advisory council, the latter having no executive authority. This kind of health department was proposed to the Massachusetts Legislature and after much discussion the bill was passed. America's first fully functioning state board of health came to an end and was succeeded by the State Department of Health. The man who did the most to get through the Legislature the bill providing for this department was Dr. Enos H. Bigelow, afterward president of the Massachusetts Medical Society, who was at the time a member of the Legislature.

### ALLAN J. McLAUGHLIN AND HIS STAFF

It goes without saying that the prime necessity in getting a new enterprise started is the right kind of person to head the organization. Massachusetts was most fortunate in getting just such a one in Dr. Allan J. McLaughlin. A man of forceful personality and extremely wide experience in public health, he had the executive ability necessary for rebuilding an old organization without in any way impairing its essential strength. Dr. McLaughlin came to Massachusetts on leave from the United States Public Health Service. Unfortunately, the exigencies of World War I necessitated his recall to Washington before the term for which he was appointed was up. Nevertheless, before he left he had placed the Department of Health firmly on its feet and, to a large extent, had charted the course it has followed ever since.

The organization of the Department of Health, as has already been indicated, consisted of a full-time commissioner, "skilled in sanitary science and

experienced in public health administration," and a public-health council consisting of the commissioner *ex officio* and six members appointed by the governor. The executive and administrative functions were centered in the commissioner, whereas the council had for its functions the making and promulgation of rules and regulations, the taking of evidence in appeals, the holding of hearings and the consideration of plans and appointments required by law. Certain divisions were established, and a system of full-time district health officers was set up.

One of the faults of the old State Board of Health had been its excessive centralization. This was remedied in the new department by the establishment of six divisions, each with a director, who, with one temporary exception, was a full-time worker. These divisions included sanitary engineering, water and sewage laboratories, food and drugs, communicable diseases, biological laboratories and hygiene. In addition, eight health districts were created, with a full-time medical health officer in each. These men were placed in the Division of Communicable Diseases for administrative purposes, but were expected to represent the commissioner in their own districts. This feature of the Department was not entirely new, since a somewhat similar system had been in effect under the State Board of Health. Beginning in 1898 with one man, there were later fifteen inspectors of health, who, however, were required to give only part of their time to this work. Much of the time of these early inspectors of health was devoted to factory inspections. With the creation of the State Board of Labor and Industries, this responsibility was transferred to the new board.

Important as were the duties of the state district health officers, there was a lack of adequate assistance. As a rule there was no local office provided and no clerical assistance. Clerical work had to be done during intervals of visiting boards of health, investigating epidemics, getting materials for case records, looking up all cases of ophthalmia neonatorum and carrying on educational work in the various communities of the district.

### COMMUNICABLE DISEASE THEN AND NOW

As an example of the tremendous problem that faced the Department in investigating communicable diseases, one may refer to an early statement of the new commissioner, allocating the annual deaths from preventable diseases in Massachusetts to the various divisions best prepared to aid in their prevention. The Division of Communicable Diseases, for example, in 1915 was charged with 15,920 deaths, which included those from syphilis, tuberculosis, pneumonia, diphtheria, measles, scarlet fever, typhoid fever, whooping cough and influenza. Later, owing to other arrangements for handling these diseases, syphilis and tuberculosis were removed from this list, leaving a total of 7920 deaths

within the province of the Division of Communicable Diseases. It goes without saying that a detailed investigation of each of these deaths would have been utterly impossible; only epidemics as a rule could be carefully inquired into. It is interesting to note that if the deaths from these same diseases had been reallocated at the beginning of 1944, the total number would have been 1020 instead of 7920. This great change in the number of annual deaths cannot, of course, be charged to the credit of the Department alone. It does, however, represent the results of the combined efforts of local and state departments of health in co-operation with the medical profession and a far better-informed public.

When the Department of Health was created, all its efforts toward reducing the incidence and death rate of tuberculosis and of the venereal diseases were centered in the Division of Communicable Diseases. Later, however, a Division of Tuberculosis was created, and much later still a Division of Venereal Diseases. In the case of tuberculosis, shortly after 1915 it was felt that better provision should be made for the hospitalization of open cases and the detection of early cases through local dispensary service. This sentiment resulted in legislation establishing county tuberculosis hospitals and extending local dispensary service. Regarding the problem of venereal diseases, which up to the time of World War I had never been adequately discussed, to say nothing of being adequately treated, a great deal of study was given to ways of remedying this condition. A plan was worked out for the reporting of venereal disease by physicians directly to the Department by means of numbers, identification by name being left as a last resort in careless or recalcitrant cases.

Another difficult problem attacked in these early years was that of milk sanitation. Milk at that time was a subject of heated controversy. Epidemics of septic sore throat were far from infrequent, yet the simple expedient of pasteurization of milk on the scale on which it is now practiced was merely a hope for the future. A valuable study of the whole question was made by a milk board made up of members of the Department, and served its purpose in bringing about a better understanding of the whole question.

#### PERSONAL AND COMMUNITY HYGIENE

The period between the establishment of the State Board of Health in 1869 and its reorganization in 1914 may rightly be called primarily the era of sanitary control of the environment. This was the period of the great progress in water and sewage purification already referred to. At the same time strides were made in the direction of adequate supervision of foods and drugs.

Beginning, however, in 1915, a determined effort was made under the leadership of Dr. McLaughlin to carry to the average citizen as much as possible

of the knowledge and practices already familiar to public-health workers, in order that the measures initiated by health officials might be better understood and receive more adequate support. Certain aspects of this educational work had to be taken to the medical profession as well, particularly in the case of ophthalmia neonatorum. At the beginning of this period, cases of ophthalmia neonatorum were extremely frequent and blindness often resulted. Years of investigation of each case of sore eyes in newborn babies and the instigation of proper treatment resulted in the almost complete disappearance of blindness due to ophthalmia neonatorum.

Infant mortality at that time judged by present-day standards was startlingly high. Approximately 10,000 infants under one year of age were lost every year in Massachusetts, as compared with about 2700 in recent years. The Department undertook to instruct parents in the simple procedures of infant hygiene and to get prospective mothers to their family physicians for prenatal care.

The need for this kind of instruction led to the first use of public-health nurses. Early in the life of the Department the Division of Hygiene employed two nurses as health instructors. Gradually the number of public-health nurses increased, and the scope of their work broadened until it became one of the most important phases of the Department's work. A beginning was also made in more highly specialized health instruction through the appointment of a health instructor in foods.

One of the most outstanding of all the special efforts directed against infant and maternal mortality was inaugurated when Dr. McLaughlin was able to bring about an alliance between the Department and certain outstanding private agencies whereby it was found possible to get together a group of eight public-health nurses whose salaries were paid by money received from the American Red Cross. Expenses were carried by the Department. A Child Conservation Committee was appointed by the commissioner, chosen from members of the Department and assisted by a large and distinguished advisory committee made up of outside specialists. Under the direction of this committee careful and detailed studies were made in each town in the Commonwealth, and after careful consideration by the Child Conservation Committee these were translated into definite recommendations to the proper authorities of these towns.

#### EUGENE R. KELLEY, THE SECOND COMMISSIONER

In 1918, to the great regret of the Department and all interested in it, Dr. McLaughlin was recalled to Washington for war duty and was succeeded as commissioner by Dr. Eugene R. Kelley, who had served with Dr. McLaughlin from the beginning as director of the Division of Communicable Diseases.

Dr. Kelley was at the time a relatively young and vigorous man who before coming to Massachusetts had served as health commissioner of the State of Washington. Imbued with the principles for which Dr. McLaughlin stood, he took up the work where the latter had left it, and carried it forward with the changes that increasing public-health knowledge and increasing public-health consciousness made desirable and possible.

The first great change came in 1919 when the Legislature decided to do away with the large number of boards and commissions that had hitherto functioned in a somewhat overlapping manner and to set up in their place a far smaller number of more responsible departments. In this reorganization the Department of Health fared extremely well. Its name was changed to that of the Department of Public Health, and it received as part of the new Division of Tuberculosis the state sanatoriums hitherto under the jurisdiction of a board called the Trustees of Hospitals for Consumptives. This division was later to have another institution placed under its care, namely, the new Cancer Hospital at Pondville.

In 1929, an outstanding attempt was made under the inspiration of Dr. Henry D. Chadwick, afterward commissioner of public health, to reach tuberculosis at its source through the early detection of the disease in children. With Dr. Kelley's backing a ten-year tuberculosis program was begun; it was usually referred to as the Chadwick Clinics and was named, of course, after the man who conceived the idea and carried it to completion.

One of the problems of a good administration has always been to get those who are interested in a given field to co-operate adequately. The great field of the health of the child has always been of interest to the people of the Commonwealth. School medical inspection began as early as 1894 in Boston, and later legislation required medical and nursing supervision of all Massachusetts school children. Two state departments in the very nature of things are deeply concerned with the health of the school child, namely, the Department of Public Health and the Department of Education. Yet for many years there was little effective co-operation between these two departments. Dr. McLaughlin was deeply concerned over this, and shortly after Dr. Kelley succeeded to the commissionership a close relation was established, whereby both departments united to stimulate local interest in the school health problem and to aid local authorities in strengthening and increasing the work already in operation. The possibilities of such co-operation are unlimited.

As time went on the need was felt for additional specialization. Increased knowledge of nutrition and of the need of doing something to cut down the incidence of the universal disease, dental caries, led to the appointment by the Department of workers who specialized in these fields and who could serve

as consultants to the more generalized staff workers as well as to local organizations. Consultants in public health nursing stimulated to a remarkable degree the establishment of new public-health nursing services in the local communities.

Early in the history of the Department of Health, it was felt that something should be done toward reducing the cancer death rate. Not much seemed possible at that time, but it was believed that it would be a step in the right direction if a free tumor diagnostic clinic were established. This was done in 1919 through the co-operation of the Harvard Cancer Commission. In 1925, the Legislature directed the Department of Public Health and the Department of Public Welfare to make a study of the cancer situation in Massachusetts and to recommend necessary measures for successfully attacking this problem. Dr. Kelley's death occurred before this study was completed, but under his successor, a report was made to the Legislature, and as a result money was appropriated for a hospital to be devoted to the treatment of cancer patients. This cancer program has grown until it now represents the larger part of the activities of a special division in the Department, which has carried on extensive statistical studies and a great deal of public education, seemingly with demonstrated success.

#### GEORGE H. BIGELOW, PUBLIC-HEALTH EVANGELIST

On the death of Dr. Kelley after eight years' service as head of the Department, his deputy, Dr. George H. Bigelow, was chosen commissioner. With a brilliant mind and an energetic temperament, Dr. Bigelow threw himself wholeheartedly into the problems confronting the Department, struggling against public inertia, sometimes with indignation and at other times with a kind of sardonic humor that included both the obstructionist and himself. The measures proposed by Bigelow were as a rule sound, and have been or will ultimately be accepted as good public-health practice. If all milk were pasteurized, unquestionably Massachusetts would be a safer place in which to live. Even now, as a result of the insistence of Bigelow and his successors and other like-minded persons in and out of the Department, about 80 per cent of the population of this state live in communities that require that the milk supply be pasteurized or certified. Over 90 per cent of the milk consumed in the Commonwealth is pasteurized. Many of the other advances made during Dr. Bigelow's commissionership are referred to elsewhere.

After eight years of active leadership, Dr. Bigelow left the Department to become director of the Massachusetts General Hospital and was succeeded by Dr. Henry D. Chadwick, who had been associated with the Department of Public Health for many years as superintendent of the Westfield Sanatorium, director of the Division of Tuberculosis

and guiding spirit in the promotion of the childhood tuberculosis program.

#### LATER MILESTONES

At this point we shall have to take leave of personalities, since all those who have been connected with the later activities of the Department are still alive. The development of the Department of Public Health has continued and parallels the general advances in public health throughout the country and the world.

One of the later developments of considerable interest was the study made in 1935 and 1936 by the Massachusetts State Health Commission. This commission was appointed by the governor and was made up both of members of the Department and of outstanding medical and public-health experts from outside the Department staff. The commission studied existing health laws and practices and made suggestions for legislation that would anticipate normal expansion for years to come. The Legislature accepted some of these suggestions, which have been translated into statutes.

The year 1934 saw the ending of the ten-year tuberculosis program. From that time on the work has been carried on in a more or less decentralized way through county and state sanatoriums. Actual or suspected cases of tuberculosis in children are followed up through examinations by a state clinic group. During the period of the demonstration program about 400,000 school children were examined, and the importance of the prevention of tuberculosis has been brought home to practically every family in the Commonwealth.

In 1935, a pneumonia study that had been begun in 1931 with the financial support of the Commonwealth Fund of New York City was concluded. At that time the Department assumed the expense of preparation and distribution of serum for the treatment of this disease. Three books on pneumonia were written as part of this study, one a handbook for physicians on the treatment of pneumonia.

Experimental work was carried on with reference to the preparation and evaluation of placental extract in the control of measles. This was financed by the Commonwealth Fund, and the work was done by the Harvard Medical School through the Children's Hospital and in co-operation with the Department of Public Health.

During this year also the cancer work was extended by the legislative provision for a cancer and tuberculosis unit to be built on the grounds of the Westfield State Sanatorium.

The year 1936 was noteworthy for the beginning of participation by the Department of Public Health in the activities provided for in the federal Social Security Act. It is difficult to estimate the potentialities for the future of this type of federal and state co-operation. It brought and continues to bring to the Department large sums of money, both

through federal grants and through state appropriations, and involves a great expansion of both personnel and activity. The latest example of this is the Emergency Maternal and Infant Care Program for the wives of certain men in the armed services of the United States. Other specific examples of the use of Social Security funds are the programs for the care of crippled children and the control of venereal disease. It is altogether too early to assess accurately the future possibilities or, for that matter, the drawbacks in this type of joint action.

In 1937, under the provisions of an act of the Legislature, the Department of Public Health obtained funds for the hospitalization of a limited number of cases of chronic rheumatism. This work has been carried on under a contract with the Massachusetts General Hospital.

In 1939, because of the appearance of equine encephalomyelitis, the Department carried out an extensive study of the mosquito situation in Massachusetts as an aid in reaching some determination as to the way in which this disease is spread. Definite conclusions will have to await further opportunities for study.

One of the newer efforts to raise the standards of public-health practices stemmed from the recommendations of the Massachusetts State Health Commission, already referred to, and had to do with the approval of bacteriologic and serologic laboratories by the Department of Public Health. Under the provisions of this statute such laboratories may apply to the Department for approval. This is purely voluntary on the part of laboratories, except in the case of those that wish to perform serologic tests for syphilis in cases of pregnancy and those wishing to qualify for performing premarital examinations. This work is going on quite satisfactorily and is meeting with a good response from the laboratories.

In 1941, legislation was passed under which hospitals are licensed by the Department of Public Health in accordance with regulations promulgated by the Department. Provision for licensing dispensaries had been made many years previously.

The Department of Public Health has now reached the point where, because of its size and its varied activities, considerably more decentralization is necessary. In view of the traditional policy of the Commonwealth to delegate in so far as possible authority in public-health matters to the local boards of health of the various municipalities, large and small, it is more or less imperative that these communities, especially the smaller ones, be able to obtain easily advice and assistance from the Department. From the earliest days of the State Board of Health, assistance of this sort has been offered, and as time has gone on, more and more facilities have been provided for this purpose. The establishment of the district-health-officer plan marked a great increase in efficiency on the part of the Department of Health. It has been found, however, that a

further step must be taken involving the strengthening of the district offices and the placing under them of all types of services that the Department has to offer to the local communities. This strengthening is progressing at a steady rate. By this and other means, it is confidently expected that the Department will be in a position to meet the many changes that the future will undoubtedly bring in the field of public-health administration.

#### SUMMARY

Seventy-five years ago, in 1869, Massachusetts established a state board of health. This was the first unit functioning from the beginning as a state board of health. It came about after twenty years of discussion following the presentation to the Legislature of a remarkable document on sanitation, largely written by Lemuel Shattuck.

The Board of Health functioned as such from 1869 to 1879 and then was merged in the State Board of Health, Lunacy and Charity. This combination lasted for seven years, but in 1886 it was seen to be desirable that the Board of Health be made independent once more.

From 1886 to 1914, the Board of Health became increasingly necessary as public-health knowledge increased; it not only played an honorable part but

added greatly to the knowledge of its time. In 1914, the board was transformed into the Department of Health, with responsibility centered in a commissioner of health. In 1919, the name was changed to the Department of Public Health, and as such it has continued to the present time.

An attempt has been made to show the progress of the public-health movement in Massachusetts by discussing the accomplishments of certain outstanding men, beginning with Henry Ingersoll Bowditch and following down through the years with Dr. Henry Pickering Walcott, Mr. Hiram F. Mills, Dr. Samuel Abbott, Dr. Allan J. McLaughlin, Dr. Eugene R. Kelley, Dr. George H. Bigelow and their successors.

A constant advance is evident, conservative but steady and paralleling the best being made in the rest of America and throughout the world. The Department is now at the height of its efficiency and opportunity for service to the people of the Commonwealth, and is looking forward to taking its part in the still greater public health that undoubtedly lies ahead.

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## ACUTE PHOSPHORUS POISONING\*

### Report of a Case with Recovery

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AT ONE time phosphorus was a common poison owing to the use of yellow phosphorus in match tips. This practice is now prohibited by law, and as a result the number of deaths from phosphorus poisoning has been greatly reduced.<sup>1</sup> Phosphorus is, however, still used in various forms of rat and roach pastes that are easily available to the pica of some children in certain environments. Several deaths of children have been reported from eating fireworks, especially the so-called "spit devil" variety.<sup>2</sup> The majority of cases of phosphorus poisoning in adults are the result of suicidal attempts, some form of rat paste or vermin killer containing 1 to 4 per cent phosphorus being used. Cases have been reported in which phosphorus was used as an abortifacient.<sup>3</sup>

#### Toxic Dose

The toxicity depends to a great extent on the physical state of the phosphorus, which governs the rate of absorption, as well as on personal peculiarities, those who are the subject of nervous diseases

probably being somewhat more susceptible than others.<sup>2</sup> Death has occurred after the ingestion of match heads estimated to contain 65 to 130 mg., but recovery has occurred after the taking of about 400 mg. In one of Smith's<sup>3</sup> cases, match heads made of yellow phosphorus were enclosed in sweets and used for homicidal purposes; although a sweet containing 200 mg. of phosphorus was taken, the patient recovered after severe symptoms.<sup>1</sup> The consensus is that a dose of 50 to 65 mg. will produce decidedly dangerous or fatal symptoms in a healthy adult.<sup>2</sup>

#### Symptoms and Signs

There are two phases in the symptomatology — a primary one due to local irritation of the gastrointestinal tract, and a secondary one due to the action of the absorbed poisons.

The primary symptoms are usually delayed for two to six hours following ingestion. They consist of abdominal pain, burning, nausea, vomiting and diarrhea. The breath and vomitus have a characteristic garlic odor, and the vomitus is frequently

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luminous. Thirst is usually intense, and gaseous eructations are frequent. Diarrhea is a variable feature, occurring in about one third of the cases; when it is present the feces may be dark and luminous.

If the patient does not succumb to shock from the immediate effects of the phosphorus, there ensues a period of two or three days when the patient shows marked improvement, following which the second stage of poisoning is heralded by nausea and by protracted emesis, which produces a blood-streaked vomitus, diarrhea and abdominal tenderness in the region of the liver. The conjunctivas and the skin become jaundiced. There are headache, weakness and malaise. There may be bleeding from the nose or vagina, and hemorrhagic spots may appear under the skin and mucous membranes. The urine becomes scant and highly colored and contains blood, droplets of free fat and albumin; the urea content is lessened, and amino acids, especially leucin and tyrosin, are present.<sup>2</sup> Lawrence and Huffman<sup>4</sup> call attention to an increase in the number of monocytes in the blood. Marked leukopenia has never been reported, so far as is known, but in the case here reported the white-cell count was 1200 on the day of admission. There is usually a definite decrease in the blood sugar, which is explained by failure of glycogenolysis, owing to liver destruction, to check the downward course of the sugar level.<sup>5</sup> The liver is usually enlarged. There is frequently slight fever, the pulse becomes rapid, weak and irregular, and the patient gradually sinks, dying within about a week after ingestion of the poison.<sup>1</sup>

### Pathology

It is clear that the post-mortem changes vary with the duration of the poisoning. The skin is jaundiced, and hemorrhagic spots may be visible over the skin. On opening the body a garlic odor may be noted, and in acute cases the stomach contents have a faintly luminous appearance. The mucous membrane of the gastrointestinal tract shows inflammatory reaction and occasionally small erosions. Patches of submucous hemorrhage may be observed. Phosphorus is one of the most potent causes of fatty degeneration, and this change is present in marked degree in the liver, kidneys, heart and even the voluntary muscles.<sup>6</sup> The nervous system is also vulnerable to phosphorus. The inferior olivary bodies and the lipophilic cells are involved early and account for the symptoms referable to the central nervous system.<sup>7</sup>

The liver shows the most characteristic changes; it is usually enlarged and of a lemon-yellow tint, it feels greasy and soft, and small hemorrhages may be seen on the surface and in the substance. Microscopically, extensive fatty degeneration of the liver cells is observed, the accumulation of fat in Kupffer's cells being an early manifestation.<sup>4</sup> The kidneys are

larger than normal, icteric in color and of a very soft consistence. They also show marked fatty degeneration microscopically.

Phosphorus may be detected in its unoxidized form for several days, and it has been found in the body after burial for a month. Scherer's test is a good preliminary one, but since it is not specific and is affected by a variety of reducing agents, it is of value only in proving the absence of phosphorus or in indicating the desirability of other, more specific tests. The most reliable test is the Mitscherlich method, which depends on separation of free phosphorus in a current of steam, where it phosphoresces. Both these tests are described in Smith's *Forensic Medicine*.<sup>1</sup>

### CASE REPORT

D. C. (K-1889), a 23-year-old, Italian schoolteacher, entered the Newton Hospital on March 3, 1944, and was discharged on March 28. The diagnosis was acute phosphorus poisoning. The past history and family history were noncontributory. Four days prior to admission, following an argument with her fiancé, the patient ingested more than a teaspoonful of a rat and roach paste that contains 2.5 per cent phosphorus and 97.5 per cent inert matter. The amount of phosphorus ingested was estimated at about 130 mg. Because of fear the patient consulted a local physician an hour later, and he suggested that milk be taken immediately. Two glasses of milk were then ingested, followed half an hour later by a drink of whisky. Three hours after ingestion of the poison the patient began to have a headache, felt dizzy and nauseated and had epigastric pain. There were frequent attacks of vomiting during the night, the vomitus appearing "bright yellow and glowing." The vomiting relieved the abdominal pain for a short time. The mouth became extremely dry. The abdominal pain soon recurred and was severe enough to cause groaning. A severe headache developed and persisted up to admission. The following night the patient felt improved enough to attend a dance. Two days later she became so dizzy and weak that she was forced to remain in bed. Marked nausea returned, with occasional vomiting, and the abdominal pain also returned. The urine became highly colored and somewhat reduced in amount. A physician advised immediate hospitalization.

Physical examination revealed an alert young woman lying in bed in no apparent acute distress. There was a faint lemon-yellow color to the skin. The conjunctivas were icteric. The pupils were equal and reacted to light. There was a small, dried, bloody crust in the right nostril. The mucous membranes of the mouth were somewhat pale. No petechiae were present. The tongue was dry, with a gray coating. The neck was not rigid, and a few nontender cervical lymph nodes were palpated bilaterally. The lungs were resonant and clear. The heart sounds were good, with a regular rhythm and a rate of 90. A soft systolic murmur was heard over the precordium and was maximum at the apex. There was moderate tenderness to palpation in the right upper quadrant of the abdomen. The liver could not be palpated. No masses were felt, and the remainder of the examination was essentially negative. The temperature was 99°F., the pulse 80, and the respirations 15. The blood pressure was 110/70. The urine showed a specific gravity of 1.022, no albumin and complete reduction of Benedict's solution (the patient had just received 1000 cc. of 10 per cent glucose solution parenterally). The sediment contained 2 to 4 red cells per high-power field and no leucine or tyrocin. The red-cell count was 4,200,000 and the hemoglobin 86 per cent. The white-cell count was 1200, with 24 per cent segmented neutrophils, 8 per cent young neutrophils and 68 per cent lymphocytes.

The day following admission, the jaundice was more evident and the patient complained of a garlicky taste in the mouth. She was still nauseated but was able to take fluids. There were two episodes of nosebleed from the left nostril. The nonprotein nitrogen was 47.7 mg. per 100 cc., the icteric index 37, and the bilirubin 9 mg. (direct). The prothrombin



time was 28 seconds (normal, 18 seconds). The urine revealed a slight trace of albumin, with 60 to 100 red cells per high-power field. A bile test was positive, and urobilinogen was positive in a 1:30 dilution. For the following 2 days the patient felt generally improved, with no complaints except tightness in the chest, tingling in the veins and slight dizziness following Pentnucleotide therapy for the leukopenia. The jaundice, however, had definitely increased. The liver was felt 2 fingerbreadths below the right costal margin.

Five days after admission, the icteric index had risen to 111, and the white-cell count to 5000. The urine was still negative for tyrosine and leucine crystals. An electrocardiogram revealed a sinoauricular tachycardia, with an occasional extrasystole. There was no evidence of myocardial damage. The following day the jaundice began to clear, and from then on the patient made an uneventful recovery. On the 18th day, the jaundice had cleared except for a slight icteric tinge to the conjunctivas. The prothrombin time was 20 seconds. A bromsulfalein test was normal. The serum bilirubin was 2 mg. per 100 cc., and the icteric index 18. The white-cell count was 9400 and the red-cell count 4,200,000 with a hemoglobin of 84 per cent. The patient was discharged improved on March 24 with instructions to return to the Outpatient Department for a follow-up.

Treatment consisted of a high-carbohydrate, low-fat diet, with daily intravenous infusions of 10 per cent glucose in saline solution. Twenty units of regular insulin was administered intramuscularly prior to the intravenous infusions. One gram of calcium gluconate was administered orally three times daily. One hundred milligrams of thiamine hydrochloride and 200 mg. of ascorbic acid were administered intramuscularly daily. For the marked leukopenia 10 cc. of Pentnucleotide was given intramuscularly three times a day for 3 days, twice a day for 4 days, once daily for 4 days, and then once every other day until the white-cell count reached 9000. The urine was maintained at pH 7.5 with sodium bicarbonate by mouth.

In addition to the treatment in this case, when patients are seen early every attempt should be made to prevent the absorption of orally ingested phosphorus. Gastric lavage should be performed even if the patient is first seen several hours after the poison has been taken. A suitable chemical antidote is copper sulfate (0.25 gm. in a glass of water), the effect of which is to envelop the phosphorus particles with an insoluble coating of copper phosphide. Oxidizing agents, such as potassium permanganate (1:1000 solution) and hydrogen peroxide (2 per cent of the official preparation), may aid the conversion of elemental phosphorus to harmless oxidation products. Following gastric lavage,

a cathartic of magnesium sulfate should be administered to cleanse the bowels.<sup>8</sup>

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Phosphorus is a severe destructive poison. It is rapidly absorbed through the gastrointestinal tract and manifests itself by fatty degeneration and infiltration of the brain, liver, kidneys and practically all the other viscera of the body. The early symptoms are usually those of insult to the central nervous system and those due to local irritant action, as in the gastrointestinal tract. Later the symptoms are those of liver destruction, with jaundice, enlargement of the liver, an increased icteric index and usually hypoglycemia. Most cases of phosphorus poisoning have terminated fatally; hence, it is essential to make a diagnosis as soon as possible and institute treatment immediately. These cases should always be considered as emergencies.<sup>9</sup>

#### SUMMARY

Acute phosphorus poisoning is described from the standpoint of toxicity, symptomatology and pathology.

A case of acute phosphorus poisoning due to ingestion of a rat paste, with an uneventful recovery, is reported.

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## MEDICAL PROGRESS

## HEMATOLOGY

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ALTHOUGH anemia is by no means all of hematology, it is often considered its most important phase. This year's review will be limited to a more or less personalized discussion of this subject.

## GENERAL CONSIDERATIONS

*Classification*

The terms "secondary anemia" and "primary anemia" must by now be considered as clearly outmoded. Since anemia is always a symptom of some underlying disorder, all anemias are necessarily secondary. If this is the case, there is no point in discriminating between primary and secondary cases. The classification of anemia on the basis of color index, cell volume or cell diameter, or all three, has become deservedly popular, chiefly because it gives orientation regarding the possible etiologic and therapeutic factors in a given case. Thus hypochromic microcytic anemia is usually indicative of chronic iron deficiency and of a probable therapeutic response to iron rather than to liver. These features are listed in Table 1.

For a complete classification, cell size and color index are, however, not enough; the important con-

which the factor of storage is affected; and multiple pregnancies, in which the developing fetus absorbs an exceptional amount of material from the mother. Single etiologic factors are by no means as important in this regard, however, as multiple causes. Thus a woman on an inadequate intake of iron does not usually develop anemia unless she also has a gastric disturbance (achlorhydria) and either many pregnancies or menorrhagia. And an individual with sprue probably not only has a deficient diet but a chronic intestinal disturbance as well.

Anemia due to a bone-marrow disturbance is normochromic and normocytic because, although red-cell production is more or less seriously impaired, the red cells that are produced are of normal size and hemoglobin content. There is likewise an associated leukopenia and thrombocytopenia, — that is, pancytopenia, — since if the bone-marrow is the site of involvement, *all* its elements are usually affected. Numerous disturbances of the bone-marrow itself are known: aplasia and hypoplasia, as with benzol and other types of chemical poisoning and the hypoplasia of myxedema and of chronic nephritis with azotemia; replacement by leukemia,

TABLE 1. *Classification of Anemias According to Cell Size, Color Index and So Forth.*

TYPE OF ANEMIA	COLOR INDEX	CELL DIAMETER (M. C. D.) microns	CELL VOLUME (M. C. V.) cu. microns	PROBABLE CAUSE	PROBABLE EFFECTIVE THERAPY
Normocytic . . . . .	0.9-1.1	7.3-7.8	85-100	Bone-marrow disturbance	Transfusions (?)
Microcytic . . . . .	0.4-0.8	5.5-6.5	65-85	Iron deficiency	Iron
Macrocytic . . . . .	Above 1.1	7.8-8.3	100-130	Liver-extract deficiency	Liver extract

sideration is the *cause* of the anemia. In every case, it is essential, preferably before therapy is begun, to attempt a definition of etiologic factors. This can generally be done if it is remembered that anemia is usually due to one of three factors: a deficiency of materials requisite for blood formation; a disturbance in the marrow; and an increased loss of the bone-marrow's finished product, the red cell, either through hemorrhage or increased hemolysis.

The deficiency anemias are caused by a variety of factors: a dietary that is deficient in iron, protein or vitamin B complex; an inadequacy of the gastric juice, which is deficient in either free hydrochloric acid or Castle's enzyme ("intrinsic factor"); chronic intestinal malabsorption, as in chronic diarrhea, sprue and so forth; hepatic disease, in

lymphosarcoma, multiple myeloma and other tumors; and diminished or inhibited delivery, as in hypersplenism (see below). The bone-marrow biopsy, whether by puncture or trephine, is of the utmost value in the differential diagnosis of these conditions.

Anemia due to excessive blood loss may be either hemorrhagic or hemolytic in type. Severe hypochromic anemia due to chronic slight bleeding from the gastrointestinal tract often remains undiagnosed, and is frequently mistreated, usually by means of continued injections of liver extract. The blood picture of chronic hypochromic microcytic anemia in association with increased polychromatophilia of the red cells, a slight increase in the reticulocytes, polychromatophilic target cells, increased platelets and a slight "shift to the left" of the polymorphonuclear cells is usually due to chronic bleeding and

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not to simple iron deficiency. Anemia due to excessive hemolysis is usually associated with a normal or increased color index, and a normal or increased cell volume in the presence of small red cells, that is, the cells are thicker than normal. Bilirubinemia is present, and the reticulocytes are greatly increased.

From the foregoing, it may be seen that, in any given case of anemia, it is necessary to determine among other things, the factors of color index, cell volume and cell size and the various etiologic factors concerned. The classification that I prefer at present is based on both these criteria. Thus a given case may be classified as follows: macrocytic anemia, inadequate intake of protein, gastric achlorhydria — that is, liver-extract deficiency or pernicious anemia; microcytic, hypochromic anemia, inadequate intake of iron, gastric achlorhydria, profuse menses — that is, chronic hypochromic, iron-deficiency anemia; or normochromic, normocytic anemia, benzol poisoning — that is, aplastic anemia.

### *Diagnosis*

The working out of the etiologic factors in a given case presenting anemia as one of its features may either be simple or quite complex. As in other branches of medicine, one has recourse to every available bit of data derived from the history, the physical examination and the various laboratory tests, including x-ray examination and the sternal bone-marrow biopsy.

From the history one learns about the diet, the matter of gastrointestinal symptoms, the question of bleeding into the skin or from various organs and such miscellaneous symptoms as glossitis, weight loss, pains in bones and fever. The family history is important from the standpoints of anemia, early graying of the hair, jaundice and so forth. When taken with proper regard to possible disease entities, a careful history often suggests the diagnosis.

In the physical examination one pays particular heed to the questions of pallor, icterus, the appearance of the tongue, the matter of enlarged peripheral lymph nodes and the size of the spleen and liver. Careful inspection of the skin and buccal mucous membranes should be made for petechiae, ecchymoses and spider telangiectasia. The remainder of the physical examination is by no means neglected because many so-called "blood cases" turn out to have a general disease, such as myxedema, nephritis or subacute bacterial endocarditis.

The laboratory data required for diagnosis may be extensive, but often a few simple tests of the blood give the probable diagnosis. The hemoglobin estimation should be done either with a well-calibrated hemometer or preferably by means of a photoelectric colorimeter. Red-cell, white-cell and differential counts are ordinarily sufficient, although in many cases it is important to know, or at least to estimate, the platelet and reticulocyte levels. Estimations of these factors are made by noting

the extent of polychromatophilia and the abundance of the platelets in the stained smear. The hematocrit is valuable from the standpoint of determination of the mean corpuscular volume and thus of the red-cell size. Bilirubin determinations are important from the standpoint of hemolysis. Many other tests are occasionally brought into play. These include determination of the hypotonic and other fragilities, the question of hemolysins and agglutinins, examination of the stools for occult blood and urobilinogen, liver-function studies and gastric analysis.

In the cases with pancytopenia, no test is of greater importance than a biopsy of the sternal marrow. In most cases, a simple needle aspiration is sufficient to make a positive diagnosis (leukemia, multiple myeloma, hemolytic anemia and so forth). Occasionally, however, removal of a button of bone by the trephine method becomes necessary, particularly when needle aspiration is unsuccessful. This is particularly the case when fibrosis, aplasia or metastatic malignancy is present. By this method the topography of the marrow and the relation of cellular elements to bone, fibrous tissue and so forth can be recognized at a glance. Metastatic nodules, clumps of Gaucher cells and diffuse myelofibrosis are readily recognized. In my own work-up of a hematologic problem, a sternal puncture aspiration is performed as a routine measure; it not only gives diagnostic help but also is of assistance regarding the pathologic physiology of various disease conditions.

### DEFICIENCY ANEMIAS

#### *Chronic Iron Deficiency*

A continued deficiency in iron results in a shortage of hemoglobin for the developing erythrocytes in the bone marrow. As a result, the normoblasts have inadequate cytoplasm and the mature non-nucleated red cells are small and hypochromic. The anemia, which is hypochromic and microcytic, is by no means the only evidence of iron deficiency, which becomes manifest as well by changes in certain epithelial structures. Thus, the skin becomes wrinkled and flabby, the hair dry and gray, the tongue red, atrophied and shiny, and the fingernails flattened. Indeed, changes of other epithelial structures, including atrophy of the esophageal mucosa with web formation and of the stomach and intestines, often occur.

A state of chronic iron deficiency is brought about in various ways — through a diet inadequate in iron-containing food, by way of gastric achlorhydria, chronic diarrhea, chronic hemorrhage or multiple pregnancies or by a combination of two or more of these factors. Fewer cases of this condition seem to turn up nowadays than formerly, perhaps because incomes are higher and dietary inadequacy is therefore lessened. One should never mistake a chronic "idiopathic" iron-deficiency state for a

reduction in hemoglobin due to chronic bleeding from the gastrointestinal tract; for this reason, studies of the stools for occult blood and careful x-ray examination of the gastrointestinal tract are important.

Chronic hypochromic anemia is far more frequent in women than in men, probably because of the drain of the monthly loss of appreciable quantities of blood with the menstrual cycle, and the loss of hemoglobin-building substances to the fetus in pregnancy. Bethell, Blecha and Van Sant<sup>1</sup> studied the dietary habits and hematologic values of a group of 484 pregnant women in two rural counties of Michigan. Although all the women were from farms and could thus presumably obtain adequate amounts of good food, only a small number met the present-day recommended allowances for pregnancy. The incidence of anemia, almost all of which was of the hypochromic iron-deficient type, was 25.4 per cent. There was a direct relation of the incidence of anemia to the degree of iron inadequacy. As the authors state:

Although, in adults, a low food intake of iron is not generally an important cause of anemia, an exception must be made in the case of pregnant women with their increased requirements. Moreover, pre-existing stores of iron are essential to meet these added needs. Therefore, it is the quantity of iron consumed before conception that largely determines later evidences of its deficiency.

Hypochromic anemia in young and adolescent women, and for which no cause is apparent, has for centuries been known as "chlorosis." Recently, the presence of complete achlorhydria in a gastric juice of low volume has been recognized as an important feature of the disorder. The lack of hydrochloric acid may result in an insufficient digestion of iron-containing food and thus in hypochromic anemia. Chlorosis has become a rarity, and male chlorosis is almost a curiosity. I have seen only one such case, that of an adolescent boy who had a hemoglobin value of less than 20 per cent and complete achlorhydria; there was rapid improvement with inorganic iron by mouth. Thomson,<sup>2</sup> however, found 9 cases of apparently idiopathic hypochromic anemia in adolescent male recruits. Pallor, a smooth tongue (4 cases), complete achlorhydria (5 cases, with hypochlorhydria in 4), apical systolic murmurs, a barely palpable spleen (4 cases), spooned nails (4 cases) and prompt response to inorganic iron were present.

The nutritional hypochromic anemias of early infancy are rather common, particularly when infants are kept too long on a low iron intake. Kracke and Platt<sup>3</sup> point out that they may be due to such factors as prematurity and disorders of the alimentary tract, including celiac disease, diarrheas and intestinal parasites.

It should be remembered that hypochromia — a low color index — indicates a hemoglobin deficiency in the presence of more or less normally productive islands of red cells. Liver extract, for all its potency

in pernicious anemia, has no effect whatever, even of an additive type, in cases of iron deficiency. Its use in such cases has little justification. Curiously enough, many cases of chronic iron deficiency are treated for months with such wholly useless medications as liver extract, vitamin pills and so forth, while treatment with iron is withheld. The place of copper in the treatment of iron deficiency in man remains extremely questionable, although the group at the University of Wisconsin has consistently maintained the value of copper in both rat and human hemoglobin synthesis. In a recent paper, Maass, Michaud, Spector, Elvehjem and Hart<sup>4</sup> present evidence that copper is similarly useful in the hemorrhagic anemia of puppies. The value of copper in the hemoglobin synthesis of milk-fed rats has recently been questioned by Smith and Medlicott,<sup>5</sup> who found that it might stimulate erythropoiesis but did not cause an increase in hemoglobin.

#### *Chronic Liver-Extract Deficiency (Pernicious Anemia)*

In this condition, a deficiency in the liver-extract principle is brought about either by a grossly deficient protein content of the diet, by a lack of production of Castle's proteolytic enzyme ("intrinsic factor") by the stomach, by a loss of the liver-extract principle from the body because of malabsorption by the intestines, as in prolonged diarrhea, or by a failure of the liver to store or perhaps to make utilizable the liver-extract principle. Although lack of the proteolytic enzyme is probably by far the most significant factor in the etiology of the disease, it is quite likely in many cases that the disease does not fully develop until some other factor, such as dietary inadequacy or pregnancy, supervenes. The ensuing deficiency in liver-extract principle not only results in a malfunctioning, megaloblastic bone marrow and macrocytic anemia but also in disorders of epithelial structures and the central nervous system. Thus, the hair becomes gray or white early in life, the tongue loses its papillae, and the spinal cord may develop subacute combined degeneration. In fact, many cases with little anemia may show a high degree of neurologic involvement. In pernicious anemia one may discriminate four more or less distinct forms: a purely hematologic type, characterized by severe macrocytic anemia and by little if any neurologic involvement; a fundamentally neurologic type, characterized by combined system disease and by little if any anemia; a refractory type, in which therapy even with huge doses of liver extract is only partially effective (in this type free hydrochloric acid may be present to some extent in the gastric juice — the "achrestic anemia" of Israëls and Wilkinson<sup>6</sup>); and a hemolytic type, in which there is unusually striking jaundice and a large spleen.

That pernicious anemia is a deficiency state cannot seriously be questioned. That it is also, at least to some extent, a hemolytic anemia, is attested by

the acholuric icterus and the high pigment output in the feces and urine. The cause of the hemolytic component remains obscure. Johnson, Freeman and Longini<sup>7</sup> present evidence that the red cells of untreated cases of pernicious anemia are unusually sensitive to the digestive products of fat and speculate that this may be one of the etiologic factors of the anemia. Many authorities believe that the piling up in the bone marrow of large numbers of primitive red cells and their forerunners results in their gradual destruction and thus in the formation of bilirubin. To my mind, this seems a more logical explanation of and one more compatible with the idea that the disease is a pure deficiency state with resultant changes in the bone marrow, epithelial structures and nervous system.

The constitutional nature of the disease is attested by its relatively high incidence in members of the same family (4 to 15 per cent in various statistics), and by its greatest incidence in blue-eyed, fair-haired people and its lowest incidence in brown-eyed, dark-haired people. In Negroes, the disease has been said to be rare. Schwartz and Gore<sup>8</sup> found that this rarity was more apparent than real, at least at the Cook County Hospital in Chicago. There, of 1000 consecutive patients with pernicious anemia entering the hospital from 1931 to 1942, a total of 93 were Negroes. The incidence of the disease in Caucasians admitted to the hospital was 170 per 100,000, contrasting with the rate of 36 in Negroes. It was found that the Negroes tended to show a higher incidence in youth and a lower incidence in old age than did the Whites.

The pernicious anemia of pregnancy is infrequent, but when it occurs, it is liable to be extremely severe and rather markedly refractory to liver-extract therapy. It has a number of atypical features — lack of outspoken jaundice, lack of outspoken macrocytosis, presence of free hydrochloric acid in the gastric juice, no neurologic phenomena and slow response to liver extract.<sup>9</sup> In a recent case, the patient walked into my office with a hemoglobin concentration of 14 per cent (2.2 gm.) and a red-cell count of 800,100. The bilirubin value was only 0.5 mg. per 100 cc., and the red-cell picture was by no means characteristic. The striking thing in the blood picture was the presence of numerous multilobulated polymorphonuclear cells (so-called "pernicious-anemia neutrophils"), and this was by far the best single clue to the diagnosis, which was substantiated by puncture of the sternal marrow. Response to massive therapy with liver extract was slow and was considerably aided by the use of several transfusions. The various clinical and laboratory features of this condition have been fully presented in a recent study by Callender.<sup>10</sup> This author points out that the theory of a temporary intrinsic-factor deficiency during pregnancy does not fit in with all the facts related to the anemia, especially since liver extract is frequently ineffective. She also emphasizes

the atypicalness of the blood picture and the great value of the sternal puncture in diagnosis.

Carter and Traut<sup>11</sup> emphasize the cardiovascular manifestations, which they state occurred in 257 of 300 cases of pernicious anemia. This figure, however, is considerably invalidated by the inclusion of "weakness" as a cardiovascular symptom and its occurrence in 231, or 77 per cent, of the cases. The authors' conclusion that all the usual criteria of cardiovascular disease may occur solely as the result of anemia is, however, distinctly valid, together with the statement that these manifestations disappear after treatment with liver extract.

The symptoms of cord involvement in pernicious anemia are well known, but those relating to the brain are often unrecognized. The patient is frequently suspicious and even paranoid. I have seen a number who became psychotic as they grew older. Some of the most profound examples of neurasthenic disability are seen in this group of cases. Adams and Kubik<sup>12</sup> studied the histology of the central nervous system in 2 cases of pernicious anemia and found that the cerebral and spinal-cord lesions were almost identical, consisting of a more or less diffuse though uneven degeneration of the white matter. Attempts have been made to explain the neural symptoms of the disease as due to a deficiency differing from that which causes the anemia. At least in human beings, no such differentiation has been demonstrated. In swine, Wintrobe and his co-workers<sup>13</sup> produced neurologic disease closely simulating that seen in human pernicious anemia by a diet deficient in pantothenic acid and pyridoxin. Macrocytic hyperchromic anemia did not, however, result.

The treatment of pernicious anemia consists in the continued and persistent use of liver extract, preferably by the injection of a highly concentrated preparation (10 to 15 units per cubic centimeter) given at frequent intervals. The interval varies from patient to patient, particularly according to the degree of neurologic involvement. With well-defined disease of the cord, overtreatment is preferable. Most patients require an injection at least once every two weeks, although some go for a month and others require weekly injections. Relapses occur in those who neglect systematic treatment. The length of time for the development of relapse is a highly individual matter that has been studied by Schwartz and Legere.<sup>14</sup> They suggest that the amount of intrinsic factor secreted by the stomach, the adequacy of the diet, the storage capacity of the liver and certain obscure factors probably influence the duration of the remissions.

A significant problem that seems to be on the increase is the development of hypersensitivity to the injectable liver extract. In some cases, the patient goes into an alarming anaphylactic state, with generalized angioneurotic edema, bronchial asthma, vomiting and diarrhea, drop in blood pressure and

so forth. Schwartz<sup>15</sup> states that allergic reactions occur in about 10 per cent of all patients so treated. In most cases, this is probably due to pork sensitization, since most liver extracts are derived from porcine livers. All that is usually required is to shift to a beef liver extract, such as the 15-unit (1 cc.) Lederle extract or the approximately 1 unit (1 cc.) Campolon (Winthrop) liver extract. Some patients become sensitized to all types of injectable liver, and in these, recourse must be had either to attempted desensitization, which is usually unsatisfactory, or to oral liver extract, oral liver or oral gastric extract (Ventriculin).

Another problem, at least for the pharmaceutical houses, is the matter of assaying liver-extract preparations. This requires the use of relapsed cases of pernicious anemia and the rigid control of such factors as the diet, previous administration of liver or liver extract, daily reticulocyte counts and the use of suboptimal doses of extract. Practically, few relapsed cases suitable for assay are seen, most of the patients having been rendered unsuitable by a previous injection of liver extract or a little liver taken a few days previously. Biologic and animal methods would, of course, be eminently desirable, but thus far no such method has proved of value. Using explants of bone marrow from normal guinea pigs, and measuring the degree of migration of cells in response to control solutions and those containing liver extract, Young and Bett<sup>16</sup> found no consistent results. They were forced to conclude that no difference sufficiently marked to be used as the basis of an assay method existed between the responses to active and inactive extracts.

The greatest problem in therapy is not, however, the use of adequate amounts of properly assayed liver extract in properly diagnosed cases of pernicious anemia, but rather the continued use of liver extract injections in patients who have absolutely no need for this material. In the last year alone, I have personally seen about 20 patients, all of them women, with what I call "Tallqvist anemia" and who have been given continued and persistent injections of liver extract for periods varying from one to twelve years. At some time or other, the patient, her family or a new doctor becomes suspicious about the need for these injections and inquires whether they should be continued. The history is usually that of emotional instability, with numerous spells of feeling "low," "without pep" and so forth. The diagnosis of anemia has been made either by the Tallqvist scale or even more simply by inspection, and the patient is then started on her career of injections. An injection is quickly followed by an improvement in general well-being, but if one or two injections are missed, the patient again feels "low" and the blood is said to "drop." Physical examination in these cases is negative; particular attention should be paid to the tongue and the vibratory sensation, both of which are

usually normal. The blood counts are normal, as they might be in a well-treated case of pernicious anemia; the sternal marrow is normal. Gastric analysis is of utmost significance from the standpoint of differential diagnosis; if it shows free hydrochloric acid, as it almost always does, the diagnosis of pernicious anemia may be discarded, together with the necessity for continued injections of liver extract. A curious commentary on this matter is that practically every patient with anemia whom I have seen in the past few years has had numerous injections of liver extract *except those who have had pernicious anemia*. These patients have usually been referred to the hospital because of the possibility of carcinoma or some other serious disease.

### Sprue

Both tropical and nontropical sprue are probably to a great extent intestinal disorders characterized by prolonged diarrhea, bulky foul-smelling stools and the development of numerous deficiencies. These probably occur because malabsorption from the bowel results in the deficient absorption of iron, liver-extract principle, vitamin B complex, the fat-soluble vitamins, including vitamin K, and calcium. The disorder is thus fundamentally different from that due to a purely gastric disturbance, such as that seen in pernicious anemia. In sprue, although glossitis and macrocytic anemia may be encountered as in pernicious anemia, there is no evidence of a hemolytic component, the central nervous system is rarely affected, the pigment output in the stool is low, and the slow response to liver extract differs greatly from the quick effect seen in pernicious anemia. Other evidences of intestinal malabsorption include an increased sugar tolerance, a diminished calcium level in the blood, at times associated with tetany, and hypoprothrombinemia. Careful examination of the small intestine by serial roentgenograms and by the "snap-shot" technic revealed changes in 8 successive cases of nontropical sprue characterized by "puddling" and the "moulage sign," together with other indications of a greatly disturbed small-bowel function.<sup>17</sup> Whether these changes are simply secondary to vitamin B-complex deficiency or, as seems more likely, to an intestinal disorder due to multiple factors is not entirely clear at present. Whatever the mechanism, these patients are difficult to treat, often being refractory to liver extract, iron, vitamins and so forth. A crude extract of liver is preferable in view of the multiple deficiencies present. Celiac disease of children is probably a closely related condition.

(To be continued)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31091

#### PRESENTATION OF CASE

A thirty-one-year-old lumber contractor was admitted to the hospital because of intermittent hematuria.

About six years prior to admission, without any preceding injury, the patient began to pass grossly bloody urine for periods of two days to two weeks at a time. The periods recurred at intervals, varying from about a week to several months and always cleared up spontaneously. They were usually precipitated by lifting heavy objects. There was no associated pain or tenderness, nor were there any other urinary symptoms.

Two months prior to admission the patient fell, striking the left flank with his elbow. One hour later he again developed hematuria, followed very shortly by severe pain in the left flank. He was admitted to a local hospital, where the hematuria and pain disappeared after several days of bed rest.

X-ray examination of the kidneys at that time revealed extensive calcification, presumably in the pyramids. He was referred to this hospital for study.

For about a year prior to admission the patient had noted blurring of vision, especially when reading. He had also complained of aching in the back and legs for about the same period of time. For seven or eight months preceding entry he had suffered with severe headaches, coming on at any time of the day and usually relieved by aspirin. There was no history of dizziness or tinnitus.

Ten years before entry the patient had had otitis media with mastoiditis, followed by a mastoidectomy.

\*On leave of absence.

tomy. About two years prior to entry he had an attack of uncomplicated "scarlet fever," but continued to work throughout his illness.

Physical examination was essentially negative. The temperature was 98.6°F., the pulse 62, and the respirations 20. The blood pressure was 145 systolic, 85 diastolic.

Examination of the blood revealed a red-cell count of 4,830,000, with 15.4 gm. of hemoglobin, and a white-cell count of 7600, with 61 per cent neutrophils. Repeated urine examinations revealed a specific gravity ranging from 1.004 to 1.010, with + to +++ tests for albumin. The Sulkowitch test for urinary calcium phosphate was + to ++. The sediment (catheterized specimen) contained innumerable white cells and an occasional red cell and granular cast. Urine cultures showed moderate numbers of colon bacilli and nonhemolytic streptococci on a few occasions and no growth on others. The serum nonprotein nitrogen was 20 mg. per 100 cc., the protein 5.7 gm., the chloride 98 milliequiv. per liter and the carbon dioxide combining power 28.2 millimols. Several blood calcium determinations ranged from 11.1 to 11.6 mg. per 100 cc.; the phosphorus was 2.7 to 3.0 mg., and the phosphatase 5.5 Bodansky units. A phenolsulfalein test revealed 90 per cent dye excretion in one hour. The blood Hinton test was negative.

An intravenous pyelogram revealed multiple fine dense irregular areas of calcification having the general arrangement of staghorn calculi in both kidneys, more marked on the right. There were no areas of calcification in the ureters or bladder. The intravenous dye was excreted promptly. The pelvis were of normal size. The calyces on the right were obscured by calcification, but those on the left did not appear dilated. The upper end of the left ureter was moderately dilated. The bones were of normal density, and no cysts were seen.

A retrograde pyelogram on the fourth hospital day revealed that the areas of calcification described were within the kidney pyramids and bulged into the calyces, especially into the upper calyces on the left and the lower ones on the right. The cupping of the minor calyces was markedly increased, but there was no appreciable dilatation. The ureters were dilated down to the bladder and were moderately tortuous.

On the eleventh hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. EDWARD C. REIFENSTEIN, JR.: This discussion can be divided into two parts — the nature of the lesions in the urinary tract, and the cause of these lesions.

The pathology in the urinary tract first indicated its presence by intermittent gross hematuria. The most frequent causes of grossly bloody urine are tumors, calculi and tuberculous infection of the urinary tract. The onset of hematuria with exertion favors a tumor or a calculus; the persistence of intermittent bleeding for over five years without other symptoms is rather against a tumor or tuberculous infection. The recent episode of pain in the left flank following trauma and the aching in the back and legs for about one year are consistent with calculi; the findings on x-ray examination of the urinary tract confirm the diagnosis. The appearance on the x-ray plates is that of small deposits of calcium in the tubules of the pyramids of both kidneys of the type called "nephrocalcinosis." I do not believe that this type of calcification has been observed in tuberculous disease of the kidney, and hence I shall not give further consideration to an acid-fast infection in the kidney. We shall assume that the hematuria is due to the nephrocalcinosis.

No areas of calcification were demonstrated in the ureters or bladder, and the pelves were of normal size. Both ureters were dilated and tortuous, findings that are rather hard to explain. There was no history of ureteral obstruction during the passage of stones, although it is conceivable that one may have been passed during the episode of left flank pain. This would not explain dilatation of the right ureter. It is also possible that congenital strictures may have been present. Dilatation of the ureters, however, does occur for reasons that are not entirely clear in connection with renal infection, and presumably this is the explanation in the case under discussion. Furthermore, the passage of blood clots would aggravate the dilatation.

It is clear that this patient had pyelonephritis: the fixation of the specific gravity of the urine, the albuminuria and the finding of innumerable white cells, of occasional red cells and granular casts and of colon bacilli and nonhemolytic streptococci are evidence of this. The satisfactory excretion of phenolsulfonephthalein dye and of the intravenous dye for the pyelogram and the relatively normal serum nonprotein nitrogen level indicate the lack of glomerular involvement. As a matter of fact, the serum nonprotein nitrogen of 20 mg. per 100 cc. is slightly above the average normal value of 15 mg., and is consistent with the chloride level of 98 milliequiv. per liter, which is on the low side of average normal (103 milliequiv.), and with the carbon dioxide combining power of 28.2 millimols,

which is slightly on the high side of average normal (25 millimols). These slight changes are probably indicative of a mild state of dehydration. They are of no importance except to indicate that the low serum protein level (5.7 gm.) is even more significant than is apparent from the comparison with the normal levels of 6.5 to 8 gm. The hypoproteinemia was presumably due to the proteinuria.

Before I discuss the cause of these lesions, I shall consider for a moment the chemical nature of the calcification in the kidneys. Nephrocalcinosis of the type present in this patient is usually due to deposition of calcium phosphate concretions in the tubules. It is probable that the calcification increased after the pyelonephritis was established. This additional growth of the calculi would also tend to be deposition of calcium, since calcium tends to be thrown out in an alkaline urine, and colon bacilli and nonhemolytic streptococci are known to split urea and form an alkaline urine.

The second part of the discussion has to do with the cause of the nephrocalcinosis and of the pyelonephritis. The first question to decide is whether the pyelonephritis preceded or followed the nephrocalcinosis. Both situations are possible. There is little evidence, however, that the pyelonephritis preceded the calculi in this patient. We have assumed that the hematuria was due to the calculi. There was no history of renal disease prior to the hematuria. Although the patient did have otitis media and mastoiditis four years before the onset of hematuria, no renal complications are noted as sequelae to these infections. It is perhaps significant, therefore, that four years after the onset of hematuria the patient had an attack of what is called "uncomplicated scarlet fever," throughout which he worked. This may have been the infection that led to the pyelonephritis, which could readily have been established in kidneys already damaged with calcification. The case report makes no reference to the status of the teeth. Examination of the x-ray films of the jaws reveals at least two apical abscesses. Since spread of infection from an apical abscess to the kidney is quite frequent, the pyelonephritis may have had its origin from the infection around the teeth. We have no way of knowing how long these abscesses had been present. It is of interest, however, that only a year after the attack of scarlet fever the patient began to have blurring vision and severe headaches, both of which could be manifestations of renal infection. These symptoms were present only about one year before admission. Some significance might be given to the systolic blood-pressure level, which was perhaps a little higher than one would expect unless the patient was beginning to develop hypertension. The finding is consistent with a pyelonephritis of rather short duration. Further evidence that the nephrocalcinosis was present before the renal infection is derived from the fact that when pyelonephritis causes cal-



culus formation in the kidney it produces an entirely different type of calcification, which is in the renal pelvis rather than in the pyramids themselves.

If we assume that the nephrocalcinosis preceded the pyelonephritis, we then have to determine why the patient developed the nephrocalcinosis. Calcium deposits in the kidney occur from a supersaturation of calcium in the urine. In the absence of infection, in general, there are four causes for such a supersaturation: ingestion of too much calcium, leading to hypercalciuria; ingestion of too much alkali, leading to an alkaline urine, which favors calcium deposition; a blood acidosis, leading to resorption from bone of excessive amounts of calcium and to excretion of excessive amounts of calcium as a fixed base to get rid of acid radicles; and excessive parathyroid hormone activity, leading to phosphorus diuresis, a low serum phosphorus level, undersaturation of the blood with respect to calcium and phosphorus, increased resorption of calcium and phosphorus from bone and, finally, hypercalciuria. Since there is no history in this case of polygalactodipsia (increase in milk intake), alkalophagia or acidosis, the first three of these causes will be dismissed.

Did the patient have hyperparathyroidism? If so, there was practically no bone disease, since the visible bones are of normal density and show no cysts, the lamina dura about the teeth is fairly well preserved, and the serum phosphatase level was practically normal (normal, 3 to 5 Bodansky units per 100 cc.), particularly if the slight dehydration is recalled. It has been well established by Dr. Fuller Albright, however, that hyperparathyroidism can exist with little or no bone involvement, presumably because the patient ingests sufficient calcium and phosphorus to maintain the blood saturation so that bone resorption does not occur. The serum calcium and phosphorus levels make a diagnosis of hyperparathyroidism attractive. The calcium levels of 11.1 to 11.6 mg. per 100 cc. are in the borderline range between normal and high values according to the laboratory methods in use before the fall of 1943 (normal, 9.0 to 10.5 mg.) and are definitely high according to the methods now in use (normal, 8.5 to 10.0 mg.). This patient was studied in 1942, so the serum calcium level must be judged by the old standard. When these values are corrected for the low serum protein level, they would average about 12.0 mg. or a little more; in other words, they would be unquestionably high. Furthermore, the serum phosphorus values were definitely low (normal, 3.0 to 4.0 mg. per 100 cc.), particularly if we recall that slight dehydration was present. The low serum phosphorus levels also make it clear that the overactivity of the parathyroid gland was primary and not secondary to renal disease, for in the latter situation the serum phosphorus level is high.

Further strong evidence in favor of hyperparathyroidism is the occurrence of nephrocalcinosis. This type of calcification in both kidneys rarely occurs except as a consequence of hyperparathyroidism. A somewhat similar picture, but with larger areas of calcification, has been observed in 2 cases with *Haemophilus influenzae* infection in the urine<sup>1</sup>; this condition is quite rare, and there is nothing to suggest it in this patient. Other conditions with calcification in the pyramids, such as mercury poisoning, late rickets and focal deposits due to colon-bacillus infection, are also extremely rare; furthermore, they do not give the finely granular calcification seen in the films of the present case. The fact that the urinary calcium excretion was not abnormally high, as measured by the Sulkowitch test, is consistent with the diagnosis, since the specific gravity of the urine is fixed in a low range. It would be of interest in obtaining further support for the diagnosis of hyperparathyroidism to know whether the patient had complained of fatigue, polydipsia or polyuria, and whether he had lost weight.

In summary, the sequence of events seems to have been: hyperparathyroidism, probably due to a small parathyroid adenoma; nephrocalcinosis, with calcium phosphate deposits; and pyelonephritis possibly due to colon bacilli and nonhemolytic streptococci as a result of the attack of scarlet fever or of spread from the apical abscesses.

A brief word about treatment is in order. As a first step the parathyroid adenoma should be removed. Then efforts should be made to improve the kidney status. This type of calcification is not amenable to surgery, but retrograde dissolution of part of the calcification might be possible with Solution M (magnesium citrate solution buffered at a pH of 5).<sup>2</sup> There is still hope that an agent may be found that, taken by mouth, will tend to dissolve the calcium by creating an acid situation in the tubules. Of course, the urinary-tract infection must be kept under control during such a procedure. Even if no attempt is made to get rid of the calcification, an effort should be made to eliminate the urinary infection. Although this is difficult to do in the presence of calculi, it has been accomplished in several cases. In particular, this patient might have been one of those in whom penicillin causes a disappearance of nonhemolytic streptococci, and then colon bacilli, which occasionally are secondary invaders, may disappear spontaneously or in response to sulfonamide therapy.

DR. BENJAMIN CASTLEMAN: Dr. Colby, would you like to comment on this case?

DR. FLETCHER H. COLBY: We occasionally see patients like this, with calcification spread throughout the kidney in such a way that it involves the parenchyma rather than the calyces and pelvis. I recently had a patient, a young man in the air



force, who presented a picture almost exactly the same as this. He had calcification spread throughout the parenchyma of both kidneys. The urine was strongly acid, and he had a colon-bacillus infection.

I was interested in Dr. Reifenstein's comments on the distribution of calcification in tuberculosis. My experience has been that calcification in tuberculosis is present anywhere in the kidney. When we see patients like this we always think that tuberculosis is one thing that we have to eliminate. I have always hesitated to eliminate tuberculosis simply on the x-ray appearance of the distribution of calcium. I may be entirely wrong, but I believe that one ought to depend entirely on guinea-pig inoculation to be sure that it is not tuberculosis, even though the patient has an accompanying streptococcal or colon-bacillus infection, which is frequent in tuberculosis.

It seems to me that we do not know the answer to this type of case, whether the disease starts as pyelitis and, as a result of long-continued renal damage, calcium is deposited or whether the calcium is deposited first as a result of the infection.

DR. FULLER ALBRIGHT: I did not know that tuberculosis would cause bilateral calcification so uniformly throughout the kidney. It is usually bilateral but not so smoothly spread.

DR. OLIVER COPE: As one would expect from what Dr. Reifenstein has said, exploration for an anatomic diagnosis was an inevitable requirement. We can sit and argue at this stage about the diagnosis but we need more positive evidence. Early operation is important from the patient's point of view because some of our best results in hyperparathyroidism have been achieved in patients who have had a mild degree of glandular disease with crippling kidney damage. The amount of kidney damage may be wholly disproportionate to the glandular dysfunction.

The surgeon likes to be asked to operate on patients with an unequivocally high blood calcium level, an unmistakably low phosphorus level and a great deal of calcium in the urine. In hyperparathyroidism, as Dr. Castleman<sup>3</sup> has pointed out, the size of the offending parathyroid adenoma is directly proportionate to the increased level of ionized calcium in the blood plasma; in a patient with a blood calcium level of 14 mg. per 100 cc. or higher one knows that the surgical problem is simple because the offending gland or glands will be at least grape size and easy to identify. The surgeon approaches a patient of this type, one having a blood calcium level just above normal, with his heart in his mouth, and as you will see in this patient I was not able altogether to swallow my heart when I had finished. I shall read part of the operative note.

The right thyroid region was first explored. A small, thin, soft gland, the right upper, was found in a sulcus of the thyroid gland posteriorly, at the junction of the

middle and upper thirds. It was the brown color of an adenoma but was too small and thin. [The color of the gland depends on the proportion of fat to epithelial cells. If it contains no fat, it is brown; the more fat it contains, obviously the yellower it is. Normal glands vary. Adenomas generally have no fat in them.] The left side was then explored. Both the upper and lower were identified. The upper was asymmetrically placed, near the inferior thyroid artery. It was of the same brown color as the right upper but was larger and firmer. The left lower was grayer in color, longer and a little softer and lay posterior to the lower pole. The lower right region was next explored, and the gland was found. It was the largest, but was the gray-greenish color of the left lower. The right lower was excised, since it was thought to be an adenoma, but after removal it seemed more like a normal gland. The left upper was then excised as the likeliest to be an adenoma, the left lower and right upper remaining intact and unbiopsied.

Thus we found the four glands; the two upper ones were brown, and the two lower were a totally different color, the color of the largest gland not being consistent with adenoma. Within the normal-sized glands in such mild cases one can often find an adenoma that does not appear on the surface. Seemingly that is what we were confronted with here.

#### CLINICAL DIAGNOSES

Parathyroid adenoma.  
Hyperparathyroidism.

#### DR. REIFENSTEIN'S DIAGNOSES

Hyperparathyroidism (parathyroid adenoma).  
Nephrocalcinosis (calcium phosphate stones).  
Pyelonephritis (colon bacilli and nonhemolytic streptococci).

#### ANATOMICAL DIAGNOSIS

Parathyroid adenoma (parathyroidoma).

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The gland that we received was quite small, and the size of the upper limit of a normal gland, and triangular. On microscopic examination, however, there was no doubt that it was an adenoma. There was a narrow rim of normal parathyroid chief cells and numerous fat cells surrounding the tumor, which had no fat cells and was composed of large water-clear cells. This type of tumor should probably be called not an adenoma but a parathyroidoma, because the cells do not form glands. This is one of the less frequent varieties of tumor that we see in this disease. The water-clear cells are enlarged vacuolated chief cells. In the usual type of adenoma, the chief cells are slightly enlarged and uniform in size and have a pale acidophilic cytoplasm. Another type is one that shows a bit more variation in the chromatin of the cells and sometimes has giant nuclei. This is the type that has been referred to by some pathologists as a parathyroid carcinoma. In our experience covering more than eighty tumors we have been unable to find a single example of parathyroid carcinoma. There have been no recurrences or evidence of metastases.

In a recent paper from the Mayo Clinic reporting 14 cases of hyperparathyroidism, 13, or 92.8 per cent, are called carcinomas.<sup>4</sup> I believe that this paper gives the public the wrong impression of hyperparathyroidism, because this condition is benign, not malignant. Their interpretation is a bit weakened by a statement at the end, "In no case in the series under study did metastases or local recurrence occur." In other words, the diagnosis was wholly based on the morphology of the cell. The evidence for the malignant character of these tumors, according to the Mayo Clinic pathologists, rests on hyperchromatism and irregularity of the size of the nuclei. They show no definite mitoses in their photomicrographs. We have seen this same irregularity in staining character and in the size of the nuclei but do not believe that this justifies tagging a patient with carcinoma. In addition, the benignity of the disease is well borne out by the results.

A true carcinoma of the parathyroid gland can occur. Most of these, however, are nonfunctioning. In the Mayo Clinic report, reference is made to the fact that a review of the literature disclosed 7 cases of functioning parathyroid carcinomas. Two of these were from the Mayo Clinic and were included in the series of 14. This leaves only 5 cases outside of the Mayo Clinic. Some time ago Dr. Cope and I reviewed the reports of these 5 cases and concluded that only 2 of them<sup>5,6</sup> were definitely malignant. It would be extremely unusual, therefore, to find carcinoma in 92.8 per cent of one series — that of the Mayo Clinic — and only 5 cases, less than 2 per cent, in the rest of the 300 reported cases. I have dealt with this aspect of the disease because I do not want you to go away with the idea that hyperparathyroidism is caused by a parathyroid carcinoma; it should still be considered a benign condition.

DR. FULLER ALBRIGHT: This case is an example of a tiny tumor, no bigger than a normal gland, that caused hyperparathyroidism. I think the point is that a normal gland is three quarters fat and one quarter epithelial cells, whereas a tumor is entirely composed of epithelial cells.

DR. CASTLEMAN: I might add that I have received a letter from this patient's physician stating that in November, 1944, more than two years after operation, the patient's general health was excellent and that he was regularly doing heavy work. It is interesting, however, that the urine was cloudy and that x-ray films still showed calcific deposits in the tubules.

DR. COPE: I am glad that Dr. Castleman has dealt with the question of carcinoma in these parathyroid tumors. I am astounded at the position taken by the physicians of the Mayo Clinic. They are calling the common benign adenoma malignant. The surgical implications that they draw are inordinate. Widespread excision, which one likes to practice in malignant disease, would be crippling to the patient.

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## CASE 31092

### PRESENTATION OF CASE

*First admission.* A thirty-four-year-old accountant was admitted to the hospital after a convulsion.

Sixteen years previously, at the age of eighteen, and many times since then, he had been refused life insurance because examination of urine revealed albumin, casts and a low specific gravity. At that time eight different physicians saw him in rapid succession and treated him with "bladder irrigations." At the age of twenty he was admitted for two weeks to another hospital, where he was cystoscoped, following which he had weekly bladder irrigations for one year. At twenty-seven he was placed on a salt-free, low-protein diet, which he disregarded. At twenty-nine he was admitted for two weeks to still another hospital, where he was given sulfathiazole, which "cleared up" the urinary-tract infection. He was apparently well for the next five years. Five months before admission he experienced severe muscular cramps in the calves and upper abdomen. At that time his physician gave him calcium lactate and iron tablets and three months later added one quart of milk daily. Two weeks before admission he developed a head cold with coryza, severe hoarseness and cough productive of bloody mucus. He spent three days in bed, the oral temperature being 102°F. While in bed his muscle cramps returned. Two days before admission he experienced two episodes of shaking of the extremities and body without loss of consciousness but with inability to grasp anything and with resultant pain and tenderness of the muscles. In the afternoon of the day of admission, while standing at a gasoline station, he had another episode of generalized shaking and fell to the ground unconscious, following which he was brought to this hospital.

At fourteen years of age he had had a tonsillectomy, and at eighteen he had been treated for gonorrhea with irrigations. He had been married twice and had two children, six and nine years of age respectively.

Physical examination revealed a well-developed, well-nourished, man showing deep regular respirations. The throat was red. The right side of

the tongue was swollen and bruised. The nasal mucosa was covered with dried hemorrhagic exudate. A few petechiae were present over the upper thorax. Breath sounds were slightly increased, with fine rales in both axillas. An apical Grade II systolic murmur was heard. The muscles were diffusely tender. A uremic odor was noted on the breath. Trousseau and Chvostek signs were negative.

The temperature was 98.6°F., the pulse 90, and the respirations 20. The blood pressure was 160 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 2,380,000, with 6.6 gm. of hemoglobin. The white-cell count was 14,700, with 77 per cent neutrophils. There was moderate variation in size and shape of the red cells. The urine was light amber and acid in reaction. The specific gravity ranged from 1.008 to 1.012, with one later specimen reaching 1.020 and one 1.004. There was a ++ test for albumin. The sediment showed 1 to 3 white cells and occasional red cells per high-power field. A Hinton test was negative. The nonprotein nitrogen was 120 mg. per 100 cc. The total protein was 5.5 gm., with an albumin-globulin ratio of 2.5. The serum sodium was 131 milliequiv. per liter, the chloride 106 milliequiv., the carbon dioxide 7 millimols, the calcium 8.6 mg. per 100 cc., the phosphorus 7.5 mg., the potassium 5.7 milliequiv. per liter, and the phosphatase 4.9 Bodansky units per 100 cc. A phenolsulfonephthalein test showed less than 10 per cent excretion in one hour. Urine culture on admission grew a few colonies of *Staphylococcus albus*. X-ray films of the abdomen were negative.

On the twelfth day the patient was put on intramuscular penicillin — 48,000 units per day for four days, 24,000 units for two days and 12,000 units for six days. Subsequent urine cultures showed no growth. On the nineteenth day he had had a severe pain in the chest, which one observer believed was characteristic of coronary occlusion. An electrocardiogram was negative. During treatment the carbon dioxide reached 31.2 milliequiv. per liter but fell back to 17 milliequiv. The serum phosphorus was elevated to 11.4 mg. per 100 cc. The nonprotein nitrogen did not change.

The patient was discharged on the thirty-fifth hospital day; he felt quite strong and much improved. During his stay he had received six 500-cc. transfusions of whole blood, as well as Citro-carbonate and calcium gluconate.

*Second admission* (two months later). Six weeks after discharge he had an episode of severe nocturnal dyspnea. He promptly developed congestive failure but responded well to digitalization. Ten days before admission he developed a cold, with fever and a cough productive of blood-tinged sputum, and a week later had another episode of severe dyspnea. During the following two days he became increasingly drowsy, continued to cough, was nauseated, vomited and had slight pain in the right chest.

Physical examination revealed a pale, dehydrated, drowsy, orthopneic man sitting upright in obvious distress; he had a strong uremic odor on his breath. The heart was enlarged in all directions. The sounds were weak, with a gallop rhythm at 120. The lower two thirds of the right chest showed dullness and diminished breath sounds and tactile fremitus. Moist rales were heard bilaterally. The pain in the right chest was severe. The liver was palpable three fingerbreadths below the costal margin. There was moderate ascites, and marked edema of the sacrum and lower extremities.

The temperature was 101°F., and the respirations varied between 20 and 35. The blood pressure was 210 systolic, 100 diastolic.

Several attempts to withdraw fluid from the right chest failed. A pericardial friction rub was constantly present after the third day. The urine was alkaline, with a specific gravity of 1.007, a + test for albumin and a few red cells and white cells in the sediment. The blood revealed a white-cell count of 44,200, with 99 per cent neutrophils, and a red-cell count of 1,840,000, with 5 gm. of hemoglobin. The nonprotein nitrogen was 200 mg. per 100 cc., the carbon dioxide, 12 to 15 millimols per liter, the chloride 91.0 milliequiv., the calcium 8.1 mg. per 100 cc., and the phosphorus 6.5 mg. Urine culture grew *Staph. albus* and nonhemolytic streptococci. The blood and sputum showed Type 1 pneumococci.

The patient was treated with intravenous fluids, sulfadiazine, transfusions, Mercupurin, digitalis, calcium gluconate, Hykinone and sedative drugs. The sulfadiazine blood level never exceeded 10 mg. per 100 cc., and the urinary output did not drop. His sensorium gradually became increasingly clouded. He was comatose and died on the eighth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. WILLIAM W. BECKMAN: It seems to me that three diseases contributed to this man's death. One of them was acute and terminal. Another, hypertensive heart disease with congestive failure, was a sequela of the third, chronic renal disease. Certainly there is enough evidence to make a diagnosis of chronic nephritis of some sort. He had a long history of continuous albuminuria, low specific gravity and casts in the urine. He evidently was having symptoms during most of this period because he consulted so many physicians.

On physical examination there was the additional finding of high blood pressure. The laboratory findings of marked anemia, albuminuria, elevated nonprotein nitrogen, elevated serum phosphorus and marked acidosis all confirm the diagnosis of chronic nephritis. It is of interest that the casts had disappeared from the urine by the time he came to this hospital. This of course is to be expected, for, as chronic nephritis progresses into the terminal stage,

the formed elements in the sediment usually diminish and frequently disappear.

One must always attempt to define the kind of nephritis. This differential is usually more academic than practical, but it has gained importance as various sorts of chemotherapy have been devised to treat pyelonephritis according to the type of infecting organism. The wide range of the specific gravity, from 1.004 to 1.020, is surprising, for one would expect a fixed specific gravity in the terminal stage of the disease. No correction was made for the albumin, however, and it is well known that unless such a correction is made the specific-gravity readings may vary markedly. There is little here to suggest glomerulonephritis. He had had a tonsillectomy, but he had had no evidence of a streptococcal pharyngitis, scarlet fever or anything that tends to dispose toward the development of glomerulonephritis. Everything seems to point to the fact that he had pyelonephritis. It would be interesting to know whether he consulted a physician at the age of eighteen for gonorrhea before he was refused life insurance, owing to albuminuria. If this had been the case it is possible that the local irritation occasioned by the irrigations might have started an infectious process in the genitourinary tract. Following the onset, whatever it was, his many physicians all seemed to think that he needed the various sorts of treatment for the urinary-tract infection that were used. He was given bladder irrigations before the time of chemotherapy, and when chemotherapy came along, he was given sulfadiazine, which was said to clear up the infection. Probably it did not. He did well following this form of treatment and had five years of freedom from symptoms. This was probably because he had become accustomed to his chronic nephritis rather than because it had been cured, although there is no way of proving that. At any rate, I think that pyelonephritis is the likeliest explanation for the chronic renal disease.

The fact that he had pains in the legs and abdomen and had an attack of pain in the chest, which was thought to be characteristic of myocardial infarction, and the fact that he had cerebral manifestations in the form of convulsions make me wonder about some generalized vascular disease, such as periarteritis nodosa. Certainly all these are symptoms of that syndrome, and in addition it would explain the petechial rash that he had at the time of the first admission. Otherwise I cannot explain the rash. One does get all kinds of skin manifestations in periarteritis nodosa. I think it unlikely, however, that a person with periarteritis nodosa could go for sixteen years with only albuminuria, and little else, to show for it. We are following one patient with periarteritis nodosa, proved by biopsy, of many years' duration who shows nothing but albuminuria. That is most unusual. Anyway, if a patient has chronic pyelo-

nephritis he has a good right to a general vascular disease in the form of plain arteriosclerosis, and I should think that that is the more probable in this case.

It is worth considering the nature of the convulsions. In uremia there are two varieties — those due to hypertensive encephalopathy and those due to tetany resulting from a low serum calcium. The low calcium in this case is probably associated both with a lowered serum protein and with definite phosphate retention. Incidentally in situations like this, when there is chronic phosphate retention, the parathyroid glands are almost invariably found to be hypertrophied. This has been interpreted to mean that these glands are working overtime in an effort to correct the derangement in calcium and phosphorus in the serum. A total calcium of 8.6 mg. per 100 cc. is hardly low enough to produce tetany, particularly in the presence of such a high degree of acidosis as is indicated by the carbon dioxide of 7 millimols per liter. Therefore, I should say that the convulsions were on the basis of hypertensive encephalopathy, although I do not know what that is.

We then come to the treatment with penicillin. That is something not too commonly done in uremia. I have a similar patient, a man with chronic uremia whom I have followed for seven years. His urine culture always grows *Staphylococcus albus*. I asked Dr. Forbes about treating him with penicillin, and she replied that it would certainly be an advisable thing to do. It might be well to have Dr. Forbes comment on that now.

DR. ANNE P. FORBES: My statement was based on the fact that we know that a chronic renal infection can lower kidney function. Since these patients have little renal tissue to spare, getting rid of the infection may relieve them of a burden that might otherwise be crippling.

DR. BECKMAN: Whether it was due to penicillin, — he received a number of other things, — the patient improved and went home feeling better. It is interesting that they treated him with alkalis in the presence of the low calcium. Alkalosis, of course, tends to accentuate any tendency to tetany. I suppose that the addition of calcium gluconate was meant to take care of this eventuality.

The attack of nocturnal dyspnea indicates that the patient had developed hypertensive heart disease and congestive failure. Although his failure improved somewhat at first it was quite definitely manifest when he came into the hospital the second time.

The final episode clearly appears to be a Type 1 pneumococcus infection of the lungs and blood stream. It is not easy to take care of such a pneumococcal infection in the presence of chronic renal disease. In addition to the therapeutic problem presented by the necessity of giving chemotherapy and fluids to a person with chronic renal disease

who is in congestive failure, another dilemma is encountered. The chronic renal disease makes it much more difficult for the body to take care of the infection, and at the same time the acute infection tends to accentuate the renal failure.

I think that this patient died of Type 1 pneumococcus infection, both in the lungs and in the blood stream, of chronic pyelonephritis, with renal failure, and of hypertensive heart disease, with severe congestive failure. I should have pointed out that I believe the large liver and the ascites were on the basis of congestive failure and that the pericardial friction rub indicates a terminal uremic pericarditis.

DR. JACOB LERMAN: While the patient was being treated in the hospital, we talked a bit about the cause of the tetany and I thought definitely when the patient was first admitted that the tetany was due to overbreathing. I do not believe we settled that point. In any case the patient got better and was treated with alkalies and calcium and the convulsions did not return.

#### CLINICAL DIAGNOSIS

Chronic pyelonephritis.  
Lobar pneumonia, Type 1.

#### DR. BECKMAN'S DIAGNOSES

Chronic pyelonephritis.  
Uremia.  
Pneumonia and septicemia (Type 1 pneumococcus).  
Hypertensive heart disease.  
Pericarditis, terminal, uremic.  
Congestive heart failure.

#### ANATOMICAL DIAGNOSES

Chronic pyelonephritis, bilateral.  
(Uremia.)  
Pleuritis, pericarditis and peritonitis, acute fibrinous, with effusion (Type 1 pneumococcus).

Septicemia (Type 1 pneumococcus).

Parathyroid hyperplasia, marked, secondary.  
Cardiac hypertrophy, hypertensive type.  
Peripheral edema.

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy of a man showed that the terminal infection was a Type 1 pneumococcus septicemia, with a shaggy fibrous pericarditis, pleuritis and peritonitis, in other words, an acute fibrinous serositis. I do not believe I have ever seen all three serous cavities affected by the pneumococcus before. I suppose that the infection started in the lung, although at the time of the autopsy we were unable to find anything definite in the lung. If there had been pneumonia, it would have resolved. The parenchyma just under the pleura showed slight chronic pneumonitis, which may have resulted from the pleurisy, although it is quite possible that there had been a localized pneumonia. The kidneys were quite small, one weighing 50 gm. and the other 90 gm. They were markedly contracted and pale and showed the characteristic picture of pyelonephritis. There was marked destruction of the tubules and glomeruli and extensive infiltration with lymphocytes and polymorphonuclears. There were tubular atrophy and compensatory hypertrophy.

Long-standing chronic renal disease frequently produces secondary hyperplasia of the parathyroid glands, and in this case all four were tremendously enlarged, weighing together almost 5 gm., which is about thirty to forty times their normal weight. They were pale gray in contrast to the brown color that one sees in primary parathyroid adenoma. Microscopically there was an increase in the number of normal-sized cells rather than the hypertrophy of individual cells that is seen in an adenoma. There was obliteration and replacement of all the fat. The heart was enlarged, weighing over 500 gm.

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## SEVENTY-FIFTH ANNIVERSARY

It is not every day that a state department of health can celebrate a diamond jubilee. In fact, it has never happened in America until now. This issue of the *Journal* carries an article outlining the history of the Massachusetts Department of Public Health during the past seventy-five years, stressing in particular the contributions made by certain outstanding medical men.

At the time of the founding of the Massachusetts State Board of Health in 1869, the term "public health" meant very little in this country. Measures for the control of communicable disease were based on beliefs rather than on knowledge. Robert Koch

and Louis Pasteur had not yet revolutionized the prevailing ideas on the causation of disease. Only in the case of smallpox was there an effective method of immunization. Public water supplies were far from safe. Sewage disposal was still largely a matter of individual rather than community responsibility.

The newly created State Board of Health attacked these problems with courage and wisdom. They pioneered so broadly and so successfully that a lasting impress was left on sanitary practice in this and even in other countries. This was made possible largely because of a group of extraordinary individuals, who devoted their best energies to the task. Chief among these early pioneers were Dr. Henry I. Bowditch, Dr. Henry P. Walcott and Dr. Theobald Smith, honored names in Massachusetts medical history.

The period from 1869 to 1914 has well been called the "era of sanitation." By the end of that period, tremendous strides had been taken through the energetic programs of Mills, Sedgwick, Goodnough and other engineers and the time was ripe for entry into new fields. When the board was succeeded by the Department of Health in 1914, which became the Department of Public Health in 1919, an expansion in the perspective of the public was taking place and new tasks were undertaken.

Emphasis in the control of communicable diseases shifted to prevention through the use of biologic products. Education of the public in matters of hygiene was recognized as a necessity. Dr. Allan J. McLaughlin, Dr. Eugene R. Kelley, Dr. George Bigelow and their successors, following in the footsteps of the original board, kept the department well up in the front line of advance in public-health knowledge and practice. Indeed, on various occasions the department led the advance, as in the cancer-control program and that for the study and control of tuberculosis in children. A constant stream of visitors from all over the world to observe the workings of an established state health organization has testified to the department's standing.

It is especially interesting to study the relation of state to local administration in Massachusetts in view of the strong home-rule tendencies of this state. The department's functions have been mainly advisory, rather than supervisory, from the beginning.

Its seventy-five years' experience furnishes material for a study of decentralized health administration, as contrasted with the more centralized forms of many other states. Some of the inadequacies of the decentralized system are apparently now coming to light as problems become more complicated because of the widening scope of medicine and public health and the increasing density of population. An arrangement that functioned satisfactorily in pioneering days may prove inadequate to cope with the problems of the future.

## MATERIA MUSICA

THE Massachusetts General Hospital in 1941 opened the doors of its new chapel, the creation of which was the "postscript" of Bishop Lawrence's long and useful life. A Hammond organ became part of the equipment of this nonsectarian sanctuary, and to it has been added an electrical record player of high quality. With also a portable instrument that can be taken to the wards, the hospital has at last, within this decade, achieved musical independence as a long step forward from the time when hired or volunteer talent was brought to its corridors on infrequent occasions.

A program is now in effect whereby regular organ recitals and occasional gatherings of whoever will for singing exercises are augmented by short concerts of electrically transcribed music at established hours each week. In this way is the chapel, although used for no set services, still further fulfilling the broad purposes of its founder.

The next step in the musical education of the institution has been, and will continue to be, the collection of a library of records — an enterprise that has gone forward surprisingly well as its needs were made known. Although now under the guidance of a music committee, this new activity is in the hands of the Occupational Therapy Department — fittingly enough, if it is conceded that the minds and emotions should be as well occupied as the hands.

No one will question the therapeutic value of music or the possibilities for its use in the hospital armamentarium that the future may bring. In the meantime the Massachusetts General Hospital

may be congratulated on the opportunities that it has been able to make available for patients and personnel, with our best wishes for continuing success in this cultural project.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**BISHOP** — William A. Bishop, M.D., of Watertown, died February 14. He was in his fifty-seventh year.

Dr. Bishop received his degree from Tufts College Medical School in 1913. He was a widely known authority in the field of industrial medicine, and for the past fifteen years had served as medical director for the American Mutual Liability Insurance Company. During World War I, Dr. Bishop served as a captain in the Army Medical Corps. He gave up his private practice last October but had continued as associate physician on the staff of the Massachusetts General Hospital. He was a fellow of the American Medical Association.

His widow and a daughter survive.

**SHAUGHNESSY** — M. James Shaughnessy, M.D., of Framingham, died February 17. He was in his sixty-fourth year.

Dr. Shaughnessy received his degree from Harvard Medical School in 1907.

His widow survives.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### EMERGENCY MATERNITY AND INFANT CARE PROGRAM

#### CONSULTANTS IN PEDIATRICS

There has been a change in the procedure concerning payment to pediatric consultants participating in the EMIC program.

The department is no longer permitted to pay a consultant's fee to a pediatric consultant when he signs the pediatric application, because he then becomes the attending physician and must be paid as attending physician according to the fee schedule. A pediatric consultant is considered to be the attending physician when the case is turned over to him for care by another physician or when the mother goes directly to him for the care of her infant.

A consultant in pediatrics who expects to be paid as a consultant should make sure that the pediatric application is signed by the attending physician and that he names the pediatric consultant on the application. The pediatrician may then be paid as a consultant to the attending physician when services are rendered.

### CO-OPERATION REQUESTED IN BLINDNESS PROGRAM

Attention is called to the law requiring the reporting of blindness in any patient examined at a clinic,

hospital or other institution or by a private physician or optometrist.

Such information is indispensable as a foundation for the development of a sound constructive program for preventing blindness in Massachusetts. As complete knowledge of the causes of blindness is vitally necessary, the co-operation of all physicians is urged in observing the law, which is as follows:

*Chapter 69, General Laws, Section 19A:* Whenever, upon examination at a clinic, hospital or other institution, or elsewhere, by a physician or optometrist, the visual acuity of any person is found to be with correction 20/200 or less in the better eye, or the peripheral field of his vision to have contracted to the ten degree radius or less regardless of visual acuity, the superintendent of such institution, or the physician, optometrist or other person who conducted or was in charge of the examination if it took place elsewhere than in such an institution, shall within thirty days report to the director the result of the examination and that blindness of the person examined has been established.

Such information should be forwarded to: Arthur F. Sullivan, Director, Division of the Blind, Department of Education, 110 Tremont Street, Boston 8. A supply of report forms may be obtained from the same address.

## COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1945

### RÉSUMÉ

DISEASES	JANUARY 1945	JANUARY 1944	SEVEN-YEAR MEDIAN
Anterior poliomyelitis	2	1	1
Chancroid	3	0	*
Chicken pox	1798	2512	2528
Diphtheria	20	24	17
Dog bite	594	460	511
Dysentery, bacillary	43	23	6
German measles	156	147	67
Gonorrhea	366	387	357
Granuloma inguinale	0	0	*
Lymphogranuloma venereum	10	0	*
Malaria	68	24	1
Measles	260	1647	1647
Meningitis, meningococcal	23	90	6
Meningitis, Pfeiffer-bacillus	4	5	3
Meningitis, pneumococcal	4	18	†
Meningitis, staphylococcal	0	0	†
Meningitis, streptococcal	0	0	†
Meningitis, other forms	4	2	†
Meningitis, undetermined	5	17	†
Mumps	2010	913	836
Pneumonia lobar	300	646	618
Salmonella infections	3	1	5
Scarlet fever	1617	1200	1162
Syphilis	358	447	417
Tuberculosis, pulmonary	217	237	237
Tuberculosis, other forms	12	17	18
Typhoid fever	2	2	2
Epidemic typhus	2	6	2
Whooping cough	613	373	881

\*Made reportable December, 1943

†Pfeiffer-bacillus meningitis only other form reportable previous to 1941

### COMMENT

Bacillary dysentery, during January, showed a marked increase in the number of cases, reaching a figure more than three times that of December and seven times that of the seven-year median.

Scarlet fever reached the highest point for any January since 1933. The cases were well scattered throughout the Commonwealth.

Lobar pneumonia dropped to the lowest January figure since reporting began.

For the second time in history no cases of typhoid fever were reported in the month of January.

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Haverhill, 1; Lowell, 1; total, 2.

Anthrax was reported from: Lynn, 1; Peabody, 1; total 2. Diphtheria was reported from: Barnstable, 1; Boston, 3; Foxboro, 1; Hull, 1; Mattapoisett, 1; Medford, 1; New Bedford, 1; Somerville, 9; Southbridge, 1; Waltham, 1; total, 20.

Dysentery, bacillary, was reported from: Beverly, 3; Boston, 7; Cambridge, 3; Lexington, 19; Malden, 2; Quincy, 1; Revere, 1; Wakefield, 4; Walpole, 1; West Boylston, 2; total, 43.

Encephalitis, infectious, was reported from: Chelsea, 1; Everett, 2; Somerville, 1; total, 4.

Malaria was reported from: Boston, 4; Camp Edwards, 8; Cushing General Hospital, 14; Haverhill, 4; Hingham, 1; Lowell, 1; Medford, 1; Melrose, 1; Quincy, 1; Regional Hospital, Waltham, 31; Somerville, 1; Webster, 1; total, 68.

Meningitis, meningococcal, was reported from: Boston, 8; Chelsea, 1; Chicopee, 1; Fall River, 1; Fitchburg, 1; Haverhill, 2; Lynn, 1; Marblehead, 1; Medford, 1; Naval Training School (Harvard University), 1; Plymouth, 1; Quincy, 1; Revere, 1; Wakefield, 1; Worcester, 1; total, 23.

Meningitis, Pfeiffer-bacillus, was reported from: Boston, 1; Bourne, 1; Salem, 1; total, 3.

Meningitis, pneumococcal, was reported from: Newton, 2; Springfield, 1; Worcester, 1; total, 4.

Meningitis, other forms, was reported from: Boston, 1; Lynn, 1; Tisbury, 1; Watertown, 1; total, 4.

Meningitis, undetermined, was reported from: Boston, 2; Chelsea, 2; Monson, 1; total, 5.

Salmonella infections were reported from Arlington, 1; Cambridge, 1; Melrose, 1; total, 3.

Septic sore throat was reported from: Attleboro, 1; Boston, 19; Everett, 1; Merrimac, 6; Millbury, 1; Norwood, 1; Watertown, 1; Whitman, 1; total, 31.

Tetanus was reported from: Grafton, 1; total, 1.

Trichinosis was reported from: Becket, 1; Boston, 4; Chelsea, 1; Shirley, 1; total, 7.

Undulant fever was reported from: Amesbury, 1; Boston, 1; total, 2.

## CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Lowell	March 2	Albert H. Brewster
Salem	March 5	Paul W. Hugenberger
Haverhill	March 7	William T. Green
Brockton	March 15	George W. Van Gorder
Worcester	March 16	John W. O'Meara
Pittsfield	March 19	Frank A. Slowick
Springfield	March 21	Garry deN. Hough, Jr.
Fall River	March 26	Eugene A. McCarthy
Hyannis	March 27	Paul L. Norton

## MISCELLANY

### ABSENTEE SICKNESS RATE SOARS

Absenteeism due to sickness among male industrial workers showed a substantial increase for the third quarter of 1944, shooting the total industrial sickness rate for the year up to 37 per cent above average for the period 1935-1944, according to statistics released by the Industrial Hygiene Division of the United States Public Health Service.

Nonrespiratory-nondigestive diseases rose 15 per cent above the same period in the previous year. Conditions contributing to this record included a 26 per cent increase in "rheumatism," a 29 per cent increase in neurasthenia and other diseases of nervous or mental origin and a 34 per cent increase in diseases of the genitourinary system. The incidences of rheumatic diseases, diseases of the heart and arteries, nephritis and nervous diseases have never been equaled or exceeded within the past decade. Nervous



diseases showed the highest rate of increase, rising 76 per cent above the ten-year mean. The rate of respiratory diseases, although slightly lower than that in 1943, was 32 per cent above average for the decade. Digestive diseases also rose to a rate exceeding anything experienced within the ten-year period.

Employment conditions peculiar to wartime are held responsible. Categories of disease showing the highest increase involve mainly older workers. The hiring of workers long unemployed or retired is one factor held to contribute to the record sickness rate, as is the employment of youths and other inexperienced personnel, and the necessity for employing in industry men rejected by the armed services. Wartime working and living conditions are also thought to be reflected, since other factors held accountable include emotional strain and personal mental conflict, overcrowding in plants and war communities, fatigue due to the lengthened work week, and night work. — Reprinted from *Industrial Hygiene News Letter* (January, 1945).

## CORRESPONDENCE

### PHYSICIANS REGISTERED IN NOVEMBER

To the Editor: Attached is a list of the physicians registered by examination by the Massachusetts Board of Registration in Medicine on November 17, 1944.

H. QUIMBY GALLUPE, *Secretary*

\* \* \*

Addes, Jacob (Middlesex University, 1944): 5123 14th Avenue, Brooklyn, New York.  
 Agrin, Irving Nelson (Chicago Medical School, 1943): 3053 36th Street, Astoria, Long Island, New York.  
 Becker, William (Chicago Medical School, 1943): 404 Hart Street, Brooklyn, New York.  
 Berkowitz, Moe (Middlesex University, 1943): 1319 Avenue P, Brooklyn, New York.  
 Boller, Raymond Jerome (New York University, 1942): 51-11 63rd Street, Woodside, Long Island, New York.  
 Camello, Albert Patrick (Boston College of Physicians and Surgeons, 1944): Holy Family Hospital, Brooklyn, New York.  
 Coggan, Manuel (Middlesex University, 1943): 84 Mt. Vernon Street, Malden.  
 Dorsey, Joseph Farrell (University of Tennessee, 1937): 1221 Forrest Avenue, Memphis, Tennessee.  
 Ehrenberg, Bernard (Chicago Medical School, 1943): 632 Union Avenue, Elizabeth, New Jersey.  
 Eyres, Alfred Ernest (State University of Iowa, 1932): Worcester State Hospital, Worcester.  
 Fitch, Edna Mae Jones (University of Wisconsin, 1943): Sturgis, South Dakota.  
 Gelbin, Milton Ruel (Chicago Medical School, 1943): Barnet Memorial Hospital, Paterson, New Jersey.  
 Goldstein, Max Richard (Hahnemann Medical School, 1943): 605 Commonwealth Avenue, Boston.  
 Henry, Herman Gordon (Philadelphia College of Osteopathy, 1943): 35 W. Main Street, North East, Pennsylvania.  
 Hindle, Joseph Anthony (Jefferson Medical College, 1940): Boston Psychopathic Hospital, 74 Fenwood Road, Boston.  
 Hughes, Paul William (College of Physicians and Surgeons, Boston, 1944): 936 N. Irving Avenue, Scranton, Pennsylvania.  
 Jacobs, John Lesh (Harvard Medical School, 1929): West Townsend, Vermont.  
 Kennedy, Raymond James (Loyola University, 1926): 509 Third Avenue, Joliet, Illinois.  
 Lazarus, Sydney Simon (Chicago Medical School, 1943): 300 Ocean Parkway, Brooklyn, New York.  
 Levenson, Stanley Mortimer (Harvard Medical School, 1941): Boston City Hospital, Boston.  
 Loebel, Arthur Louis (Chicago Medical School, 1943): 1690 President Street, Brooklyn, New York.  
 Meyer, Manfred (University of Halle-Wittenberg, 1920): 41 Waltham Street, Boston.  
 Moldin, Sidney (Middlesex University, 1944): 141 E. Ravenwood Avenue, Youngstown, Ohio.  
 Murray, Oscar Beryl (University of Georgia, 1933): 605 Commonwealth Avenue, Boston.

Pross, Philip (Middlesex University, 1944): Wilmington General Hospital, Wilmington, Delaware.  
 Rettew, Philip Lewis (University of Pennsylvania, 1941): 605 Commonwealth Avenue, Boston.  
 Ross, Jasper Newton (University of Illinois, 1941): 17 Bowker Street, Brookline 46.  
 Schnall, Meyer DeWitt (Johns Hopkins University, 1942): 810 Madison Avenue, Bridgeport, Connecticut.  
 Schwartz, Oscar (Chicago Medical School, 1943): 1020 45th Street, Brooklyn, New York.  
 Sherwood, Harold R. (University of Arkansas, 1939): 605 Commonwealth Avenue, Boston.  
 Smoley, Melvin (Chicago Medical School, 1943): 212 West 22d Street, New York City.  
 Svenson, Orvas (Harvard Medical School, 1937): 2 Netherlands Road, Brookline.  
 Tauber, Hans (Middlesex University, 1943): 87 Hamilton Place, New York City.  
 Trevor, William (University of Maryland, 1940): 186 Commonwealth Avenue, Boston 16.  
 Turteltaub, George Nyles (Middlesex University, 1944): 1505 Ocean Avenue, Brooklyn, New York.  
 Waldman, Hyman (Middlesex University, 1944): 76 Verndale Street, Brookline.  
 Walker, Richard Parish (University of Tennessee, 1937): 37 Carlton Street, Brookline.  
 Wein, Eber Abraham (Chicago Medical School, 1943): 565 Manhattan Avenue, New York City.  
 Weissman, Morris Paul (Middlesex University, 1942): 1395 Eastern Parkway, Brooklyn, New York.  
 Woronoff, Morris (Middlesex University, 1943): 570 Lefferts Avenue, Brooklyn, New York.

## NOTICES

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 8

##### FRIDAY, MARCH 9

\*9:00-10:00 a.m. Protein Nutrition in Problems of Medical Interest. Dr. Fredrick J. Stare. Joseph H. Pratt Diagnostic Hospital.  
 10:50 a.m. Tuberculosis of the Skin. Dr. G. Morris. (Postgraduate clinic in dermatology and syphilology.) Amphitheater, Mallory Building, Boston City Hospital.  
 12:00 m. to 1:00 p.m. Clinicopathological conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

##### SATURDAY, MARCH 10

\*10:00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

##### MONDAY, MARCH 12

\*12:00 m.-1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

##### TUESDAY, MARCH 13

\*12:15-1:15 p.m. Clinicorontgenological conference. Peter Bent Brigham Hospital.

##### WEDNESDAY, MARCH 14

\*9:00-10:00 a.m. The Glaucoma Problem and General Medicine. Dr. Joseph Igersheimer. Joseph H. Pratt Diagnostic Hospital.  
 \*12:00 m. Clinicopathological conference. Children's Hospital.  
 \*12:00 m.-1:00 p.m. Clinicopathological conference. Cambridge Hospital.  
 7:15 p.m. Graduate seminar in pediatrics. Children's Medical Service. Amphitheater 3A, Massachusetts General Hospital.

\*Open to the medical profession.

MARCH 8. Certain Neurological Problems as Regards Children: Diagnosis and treatment. Dr. Franc D. Ingraham. Pentucket Association of Physicians. 8:30 p.m. Haverhill.  
 MARCH 14. New England Pediatric Society.  
 APRIL 30. New York Institute of Clinical Oral Pathology. Page 120, issue of January 25.  
 MAY 22-24. Hotel Statler, Boston. Annual meeting of the Massachusetts Medical Society.  
 SEPTEMBER 17. American Public Health Association. Page 752, issue of November 30.

### DISTRICT MEDICAL SOCIETIES

#### PLYMOUTH

MARCH 15. Goddard Hospital, Brockton.  
 APRIL 26. Toll House, Whitman.  
 MAY 17. Lakeville Sanatorium, Lakeville.  
 All meetings will be held at 11 a.m.

#### WORCESTER

MARCH 14. Worcester Memorial Hospital.  
 APRIL 11. Hahnemann Hospital, Worcester.  
 MAY 9. Annual meeting.

# The New England Journal of Medicine

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Volume 232

MARCH 8, 1945

Number 10

## EPOCHS IN THE HISTORY OF THE WORCESTER DISTRICT MEDICAL SOCIETY\*

ROY J. WARD, M.D.

WORCESTER, MASSACHUSETTS

WE ARE now living in an age of science. Of all the sciences none have affected the welfare and happiness of the ordinary man more than has the science of medicine.

At the time of the founding of the Worcester District Medical Society, whose one hundred and fiftieth birthday is being celebrated tonight, medicine was just beginning to feel its growing pains. For years, prior to 1794, periodic epidemics of smallpox, diphtheria, typhoid fever, cholera and yellow fever had swept over Europe and America, threatening the lives of everyone. Today, we no longer wilt before the ravages of such epidemics. We have learned to control pain, wound infection, hemorrhage and shock. Tuberculosis and pernicious anemia, which were always fatal, are now responding to treatment. It is my purpose to give a picture of this district in 1794, and to trace the part that the physicians of this community played in this remarkable achievement of medical science.

In preparation, I have reviewed historical papers from the pens of Drs. Samuel B. Woodward, Homer Gage, Lemuel F. Woodward, Albert C. Getchell, Lester C. Miller and Albert M. Shattuck. Dr. Thomas H. Gage wrote the first historical sketch in 1854, but intense search for it has failed to locate any copy. I am also indebted for the splendid help that I have received from the staff of the American Antiquarian Society and its director, Mr. Clarence D. Brigham. Dr. William F. Lynch, chairman of the Anniversary Committee, and Dr. John Fallon, the librarian, have aided in collecting material and have been generous in constructive criticism; both have been an inspiration.

On December 16, 1794, forty-one physicians assembled at the United States Arms Hotel to form the Worcester Medical Society. Thirty-six of them rode into Worcester on horseback. They came from as far west as the Connecticut River and as far east as Mendon. Only one of them, Dr. John Frink, of Rutland, was a member of the Massachusetts Medical Society, and only one ever had at-

tended a medical lecture or a medical school. They came as a protest against the Massachusetts Medical Society, which had limited its membership to seventy and in thirteen years had elected to membership only one man from west of Framingham.

Worcester, a town of 2000 inhabitants, was selected as the meeting place, not because of its size, — for Charlton and Sutton were larger, — but because it was on the stage route between Boston and New York, and because the United States Arms Hotel was the best hotel in the county. Except for the stage route, roads were very poor. Many were mere bridle paths. Only the wealthy owned a wheeled vehicle or chaise; hence, everyone walked or rode horseback.

The early records tell little about the medical problems discussed at the meetings of those days. It is known that they took the form of case reports, which today constitute a favorite method of presenting medical subjects. It is also known that Worcester County at that time was in the throes of an epidemic of smallpox, meningitis and dysentery, and that smallpox alone killed  $\frac{1}{4}$  per cent of the population.

The study of medicine at the time of the founding of this society was almost entirely by the preceptor system. Harvard Medical School had been in operation for twelve years, but by 1793 had graduated only ten students,<sup>†</sup> so that the preceptor system was the only one available to the majority of students. Dr. Samuel B. Woodward in his oration before this society in May, 1893, gave an interesting story of the mechanics of that system that is worth quoting in its entirety.

Each . . . [student] had studied with a preceptor, a plan not yet entirely given up as a part of a medical education, and at that time the only plan practicable.

A typical description shows that studying with a country doctor in 1790 meant chiefly "the care of the doctor's horse, doing chores about the house, attending the instructor in gathering and drying the herbs and simples, preparing the powders and the pills and, on rare occasions, helping in some minor surgical operations."

\*By the act of Legislature incorporated the Massachusetts Medical Society in 1780, the Society was empowered to examine applicants for license to practice medicine in the Commonwealth. Harvard Medical School was given the same right for its graduates.

\*Fifty years after the founding of the Worcester District Medical Society, in 1944, the Society was incorporated as the Worcester District Medical Society.

An indenture of 1760, quoted by Norwood, sheds such light upon the position of the apprentice, showing that the student's relations with his instructor were not in truth always and entirely one sided.

... during all which Term [four years and six months] the said Apprentice his said Master well and faithfully shall serve, his secrets keep, his lawful commands everywhere obey. He shall do no damage to his said Master, nor see it to be done by others, without letting or giving notice to his said Master. He shall not contract matrimony within said term. At cards, dice, or any other unlawful game he shall not play, whereby his said Master may have Damage. He shall not absent himself day or night from his said Master's Service without his leave, nor hant Ale houses, Taverns, or playhouses, but in all things, as a faithful Apprentice he shall behave himself toward his Master all during his said term. And the said Master, during the said term, shall by the best of his Means or Methods, Art and Mysteries of a Physician and Surgeon, as he now Professes Teach or cause the said Apprentice to be taught to perfection in consideration of the sum of One Hundred Pounds Lawful money of New York to him in hand paid. . . .

And the said William Clark acknowledges himself herewith contented and the Receipt thereof. And the said Master is to provide his said Apprentice with sufficient Meat, Drink, Washing and Lodging and Mending his said clothes, within the said term, and the said James Hubbard is to find him in wearing apparel during said term aforesaid. . . . At the end of Said term the Said Master shall and will give unto the Apprentice a new set of surgeons pocket instruments, Solomon's Dispensatory, Quences' Dispensatory, and Fuller on Fevers, and for the true performance of all and every of the said covenants: . . .

It was also customary to furnish the embryonic doctor with a certificate setting forth . . . "Mr. John Smith hath served as an apprentice to me for nearly four years, during which time he was constantly employed in the practice of Physics and Surgery, under my care, in which character he always behaved with great fidelity and industry. . . ."

Fortified with a like testimonial each man did set himself to work.

Dr. Austin Flint, of Leicester, was conducting a hospital in Worcester County for the inoculation of smallpox, and later was the first physician in the district to use the new method of vaccination with cowpox. Such subjects as these must have been uppermost in the members' minds and have made up the discussions of these early meetings. They were also looking into the future, for one of the most important actions of the newly formed society was to raise the educational requirements for the study of medicine, demanding a knowledge of Latin, Greek, elementary mathematics, natural history and natural philosophy.\* This was just ninety years before Harvard Medical School required as much.

\*Article 17 of the Laws and Regulations of Worcester Medical Society, adopted January 20, 1795, reads as follows:

"In order that the education of pupils should be more uniform and reputable it is the sense of this organization that before a person be qualified to enter upon the study of physick it is necessary that he have not only an accurate knowledge of his native tongue, but so much of the Latin and Greek as to translate them by the help of a dictionary, together with a knowledge of at least the elementary parts of mathematics, of natural history and of natural philosophy. . . . Before any pupil offer himself for examination, the physician who recommends him shall be certain that he has such a knowledge of anatomy as is necessary to understand the animal economy, its sound and morbid state, likewise an acquaintance with disease and the usual method of treating them, also a knowledge of the principles of chemistry, materia medica and the operation of medicine. As the art of physick is a mystery concerning which

In 1798 the problem came up of providing for a library, and Dr. Elijah Dix, an active physician, an apothecary and an extensive real estate dealer, offered to give 50 pounds to the society for the purchase of books.



FIGURE 1. Daniel Waldo.

chase of books. This offer was accepted and a librarian was duly elected. Thus our library dates from this offer made in 1798, although Dr. Dix failed to keep his promise to provide the money for purchasing the books.

In 1804, after ten years' struggle with the Massachusetts Medical Society, that society's charter was so modified as to admit any respectable member of the profession. It also provided for district societies, and the Worcester Medical Society was the first one to join as a body.

In 1823, a campaign was started to raise a fund for more books for the library, and a generous subscription was received from Mr. Daniel Waldo (Fig. 1), a well-to-do merchant and importer owning

those who are not medically educated have not the means of judging so as readily to distinguish between the real physician and the imposing pretender, it appears highly reasonable that some criterion should be established by which those who are qualified for practice may be known, and in order, therefore, to prevent impositions whose consequences may prove so fatal and to assist mankind in forming a judgment in a matter to them so important, this Association declares it as their decided opinion that no physician ought to be encouraged in his profession unless he has passed an examination before some regularly appointed judges. The advantage of teaching physick by lectures is confessed by the usage of all Europe but has never been enjoyed among us until within a few years. We being persuaded that great advantage will result from such systematic mode of teaching all the branches of the medical art do hereby recommend to all such as are or may become our pupils to attend the medical lectures which are annually given at the University of Cambridge."

stores in Worcester and Boston. This was supplemented by a loan of fifty books from the Boston Medical Library. From then on the fortunes of this society rose and fell with the interest shown in the library. The records show that the library was moved from place to place because of the lack of a permanent home. When dust gathered on the books and they were scattered through the houses of the members, interest in the society also waned.

In 1845, Mr. Daniel Waldo left by will, among other benefactions, including a gift to the Mas-

sachusetts General Hospital, \$5000 to this society "for the purchase of costly but useful inventions for surgical purposes, and for books treating on medical subjects . . . to the end that the science of medicine . . . may be more fully understood and the community benefited by able and enlightened physicians and surgeons." The books purchased from this fund increased the problem of a suitable place to house them. Dr. John Green offered a room, free of rent for a year, over his apothecary shop, on Main Street. This is the room Dr. Green who left the bulk of his fortune to found the Worcester Public Library. He evidently had his peculiar view as illustrated by a sketch of the library room on Main Street (Fig. 2). His testament, in 1845, shows that he covered the whole medical field. It is also recorded that he, with a Dr. Nathan S. May, took the Worcester District Society to the Worcester

physician who came to town. Dr. Samuel B. Woodward is authority for the story that Dr. Homans, father of Dr. John Homans, of Boston, was one of these, and that Dr. Joseph Sargent was the first physician who succeeded in breaking down this monopoly.

At the opening of the Free Public Library in 1861 the books of the society were moved to comfortable rooms on the first floor, where there were ample bookshelves and room to hold the meetings. It was during this time that the library was considered the peer of any medical library in the country. It

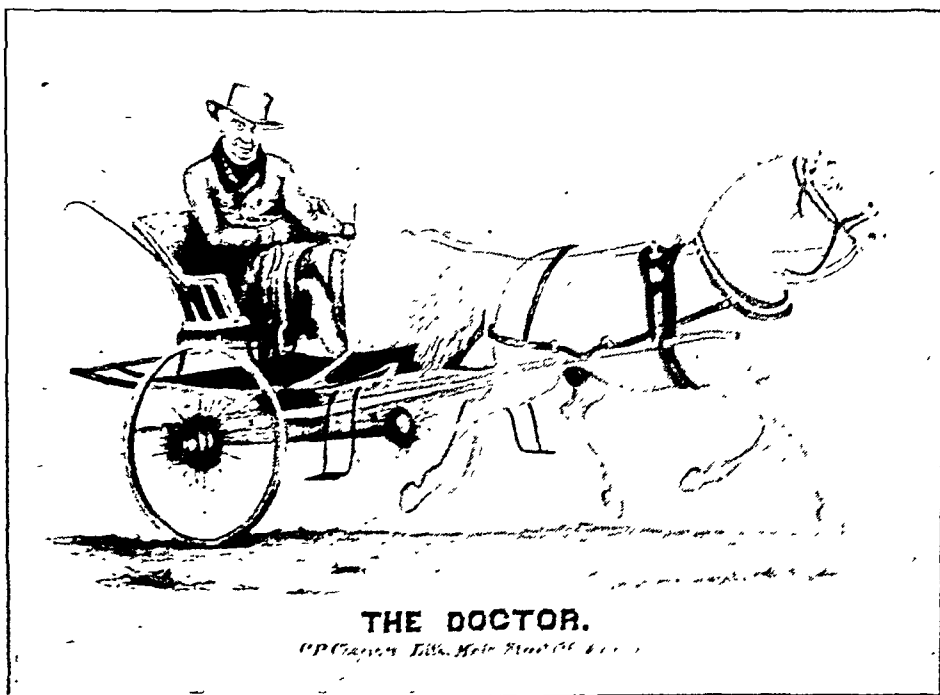


FIGURE 2. A Characteristic Pose of Dr. John Green.

sachusetts General Hospital, \$5000 to this society "for the purchase of costly but useful inventions for surgical purposes, and for books treating on medical subjects . . . to the end that the science of medicine . . . may be more fully understood and the community benefited by able and enlightened physicians and surgeons." The books purchased from this fund increased the problem of a suitable place to house them. Dr. John Green offered a room, free of rent for a year, over his apothecary shop, on Main Street. This is the room Dr. Green who left the bulk of his fortune to found the Worcester Public Library. He evidently had his peculiar view as illustrated by a sketch of the library room on Main Street (Fig. 2). His testament, in 1845, shows that he covered the whole medical field. It is also recorded that he, with a Dr. Nathan S. May, took the Worcester District Society to the Worcester

was in this location that the society flourished until 1850, when, owing to overcrowding, the books were moved to the attic. This was unfortunate. The space under the mansard roof was dingy, dirty and accessible only by a crooked ladder. There was not room enough for medical meetings, and the library died.

In 1861, the library was again asked to move. Under the leadership of the Library Committee, consisting of Drs. A. B. Marsh, Robert L. Hunt and John Patton, a new home was found at 34 Elm Street. It's example, constructed from up the ready-made materials, but owing to lack of money most of the books were left lying in bundles in the basement. In a part of the restoration of the library a new corporation was formed, the Worcester District Library, incorporating, including all members of the society.

In 1861, Dr. Green, in his annual address,

suggested a building to house the library and all the society activities, and he frequently suggested a site for such a building, but the time was not ripe. In 1935 he again made the same suggestion. Even

raised it still higher to provide a yearly nest egg. Thus, the members at home have pledged themselves to carry the financial burden for their comrades in arms.

In 1942 the library again moved. The trustees were in a dilemma. They searched the city for an available place. Many sites were found and abandoned because of expense. Then the Blood Bank Committee came forward with a proposition that the library share a small part of their building (Fig. 4), and sold to it one seventh of their building, in which it is now located, in crowded but useful quarters.

In 1906 a group of physicians and lay people organized, under the auspices of the Fresh Air Fund, the Clean Milk Stations Committee. Since mortality records were first kept it had been noted that the death rate among infants was extremely high during the summer months, and physicians were accustomed to postpone their vacations until the fall in order to care for the large number of gastrointestinal cases that were the cause of this mortality. The success of this initial effort to combat the disease was so obvious that the society voted to organize the Medical Milk Commission, to encourage the production of certified milk. This commission still is functioning and has been a large factor in saving hundreds of children's lives.

In 1936, this society blazed a new trail. Inspired by Dr. Arthur M. Kimberly, the *Worcester Medical News*, now under the guiding hand of Dr. Francis J. Steele, was started. It was the first modern district-society journal in Massachusetts and is now demonstrating its worth every month. Ninety years ago the Worcester Medical College published a medical journal extolling the virtues of the Thomsonian system of medicine, (Fig. 5).

It has been said that the modern hospital is the greatest clinical laboratory that society possesses, and that to it is owed most of the advances in medicine that have taken place. The Worcester District has not lacked in this respect. It has the first hospital ever built by tax funds for the care of the insane. This hospital was constructed by the State in 1832 on land provided by the city on Summer Street. Its first superintendent, Dr. Samuel B. Woodward, was the ancestor of the famous Woodward medical family, of whom the present Dr. Samuel B. Woodward survives. The latter is the authority for the following story of the opening of the hospital. Patients were admitted from all over the State—some from almshouses, jails and dungeons, where they had been kept under restraint. One man was brought chained inside of a wooden cage on a cart. When the new superintendent ordered the attendants to open the cage and unchain him, they remonstrated, but instead of attacking them, the patient knelt and raised his hands to worship Dr. Woodward, thinking that he must be God.

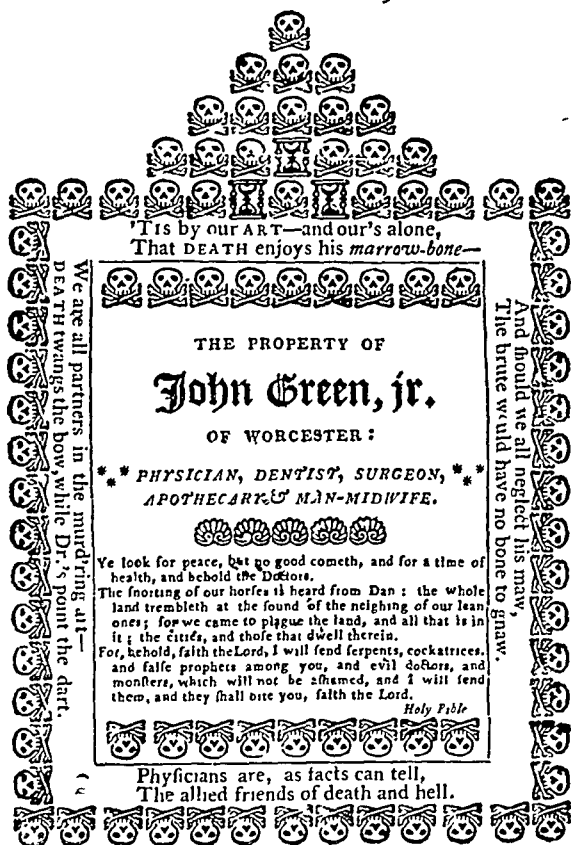


FIGURE 3. Dr. Green's Bookplate.

when the library was adequately housed at 34 Elm Street only half the members paid their dues. It was a battle to keep the rent paid, and only the most valuable of the magazines were bound. An \$18,000 appropriation was secured through the Works Progress Administration and the books were recatalogued and new stacks built, but finances continued to be a constant worry to the trustees. At their instigation a committee was appointed that, under the able leadership of Dr. Joel Melick, arranged a benefit lecture by Mrs. Franklin D. Roosevelt on "Peace." This was a financial success and was followed by three other benefits. These might have been continued had not the war intervened. More than \$6000 has been raised by this method, most of which has been put away for a building fund.

With the advent of the present war the problem of financing the activities of the society and the library increased. One third of the members had entered the armed forces. An unprecedented budget was brought in, large enough to cover not only the old but also some new activities. This was presented with trepidation, but the members themselves

In 1864, the United States Army opened the Dale General Hospital (Fig. 6) on Union Hill, occupying part of the buildings formerly used by the Worcester Medical College. Built to accommodate 1000 beds and with fourteen one-story wards, it was never filled. It was later abandoned after a vain attempt was made by the Federal government to have the city or state take it over. In 1867, Reverend John J. Powers opened a small hospital that was operated by the Sisters of St. Anne's Convent—interestingly enough, for poor patients who prepaid a small amount each year.

Dr. Peabody, former superintendent of the Worcester City Hospital, is the authority for the statement that it was done in the Clinton Hospital.

To Dr. Frank Washburn must be given the credit for establishing the Holden Cottage Hospital, a model of its kind and already so useful in its community that it is taxed beyond capacity.

Time does not permit enumerating the seventeen hospitals that have been established in this district since that early beginning on Front Street. Since then a magnificent system of hospitals has grown up all over the district, in large and small



FIGURE 4. Home of the Worcester Medical Library, Incorporated, and the Blood Bank.

In 1871, on the recommendation of Dr. Albert Wood, Worcester established the City Hospital at Front and Church streets, in the Abigail Bigelow House, with accommodations for eight or ten patients. Dr. Leonard Wheeler was the first superintendent and insisted on clinical records being kept, much to the displeasure of his visiting staff.

One of the first community hospitals to be started in the surrounding towns was at Clinton. In 1888, the Clinton Hospital Association opened its doors in a rented tenement for the admittance of its first patient, who promptly died. Discouraged but not disheartened, the association grew by dint of hard work, and now has an up-to-date hospital of seventy-four beds. Dr. Walter P. Bowers has been the president of the corporation for fifty years. Although there is some debate regarding where the first hysterectomy in the district was performed.

towns as well as in the city. Of the 6629 beds now available nearly half are outside the city limits. The rapid spread of community hospitals has added a great deal to the comfort and safety of the countryside.

The onset of the present war and the increasing use of blood for transfusions demonstrated the need of a supply for this district. At the January, 1942, meeting of the society, the pathologists of the city, Drs. Raymond Goodale, James Beck, William Moran and William Freeman, suggested the appointment of a committee to establish a blood bank. Headed first by Dr. Walter C. Seelye, and later by Dr. Edwin R. Leib, as president and Dr. William Freeman as secretary and director of the laboratory, the committee purchased a building, reconstructed it, installed equipment and has processed blood from 5000 donors. Both whole blood and blood plasma

are now distributed through twenty-four stations throughout southern Worcester County. The Cushing General Hospital at Framingham and the Lovell General Hospital at Fort Devens are

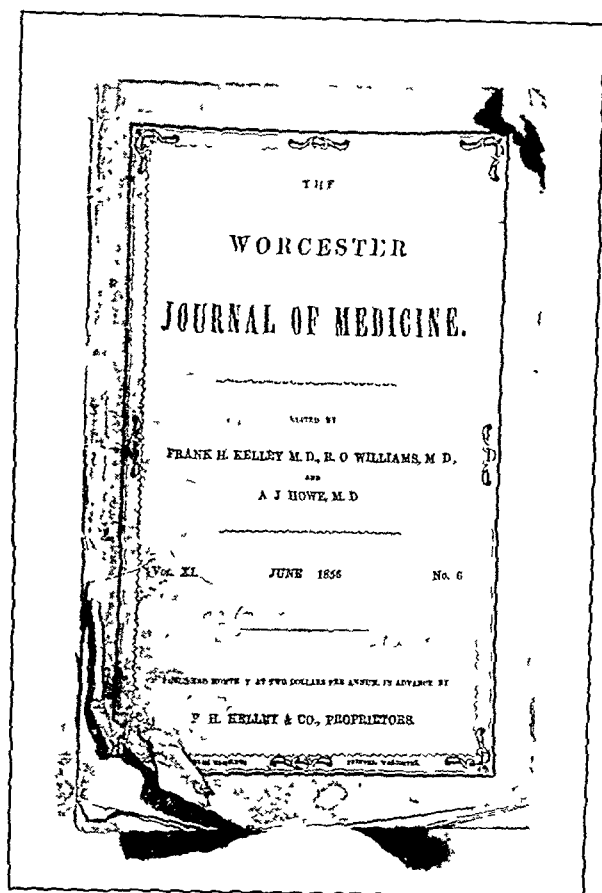


FIGURE 5. *The Cover of an Issue of the Worcester Journal of Medicine.*

also supplied. This outstanding voluntary effort on the part of the committee has been ably seconded by a splendid group of lay workers and donors, without whose aid it would have been difficult to carry on.

In 1869, the State Board of Health, the first of its kind, was established at Boston. Nine years later a city board was established in Worcester, with Dr. Rufus Woodward as the first secretary and executive officer. Since then, under the leadership of the medical profession, it has steadily increased its usefulness. One of our members, the late Dr. Thomas Kenney, was instrumental in reorganizing the setup. He built a \$1,000,000 addition to the Putnam Division of Belmont Hospital and pushed through, against considerable opposition, a plan for immunization of the school population against diphtheria, which has saved thousands of lives.

In 1894, the Health Department established a laboratory for the examination of sputums for

tubercle bacilli and cultures for diphtheria bacilli. This was the first municipal laboratory in New England and one of the first in the country after that begun in New York City. It was the beginning of a concerted attack on these two diseases in the district, which has led to remarkable results. A statistical study made some time ago revealed the fact that this city has been made the richer by \$10,000,000\* over and above the cost of the department during the last twenty years because of the prevention of sickness and the saving of lives.

During the earliest days the Worcester District Medical Society met alternately in Rutland and Worcester. Later most of the meetings were held in various halls and clubrooms about the city, except in the period 1861-1899, when the meetings were held in the Worcester Public Library. It was often recorded that after the morning session the society adjourned for dinner at the American Temperance House on Foster Street (Fig. 7). For several years the society met occasionally at various hospitals, but a great stride forward was taken in 1923 when, during Dr. A. W. Marsh's presidency, the meetings were transferred to the hospitals in the district. This was a great boon to both interest and attendance.

With the multiplication of activities by the society the officers have come to lean more and more on the assistant to the librarian, first Mrs. Barbara McPherson and now Mrs. Marjorie Edwards. In addition to her duties in the Worcester Medical Library, the assistant is a great help to the secretary, the treasurer and the editor and business manager of the *Worcester Medical News*. Her services have been increasingly valuable to the whole society.

No history of the society would be complete without at least mention of some of the controversies that took place. Opposition to homeopathy and eclectic medicine raged in Worcester as it had all over the country for twenty-five years, from 1852 to 1877. Many men were expelled from the society for practicing these systems or consulting with their practitioners.

In 1845, Dr. Calvin Newton, a graduate of Berkshire Medical College, erected on Union Hill a large building where he established his Botanico-Medical College. This building, later part of the Dale General Hospital and now Davis Hall at Worcester Academy, was built by funds subscribed by friends of the eclectic or Thomsonian system of medicine. The name of the school was changed from time to time, finally ending as Worcester Medical College. It received a charter from the Legislature in spite of strong opposition from the Massachusetts Medical Society, and for a while had a large group of students. There were six physicians and scientists on

\*This study was made by me in conjunction with a paper read at a meeting of the Worcester District Medical Society in September, 1940. The figures were studied by Dr. H. L. Lombard, of the State Department of Public Health, who said "Your figures are, too low. This goes to show that public-health work pays dividends."

its faculty who gave courses of lectures of fourteen weeks, beginning each March. The tuition was \$50, with an additional fee of \$25 for an elaborate diploma. Dr. Newton died in 1853, and with him collapsed his college and its medical magazine. The Middlesex University College of Medicine now operates under this charter. Dr. Newton, at one time a member of the Worcester District Medical Society, was expelled for violation of its bylaws.

In Hersey's *History of Worcester*, published in 1862, there were listed twenty-six allopathic, four eclectic, four homeopathic, one Thomsonian and four female physicians. In 1904 Dr. Homer Gage,

civic affairs. He was for years a member of an important committee of the parent society, the Committee on Ethics and Discipline. The second was Dr. Edwin B. Harvey (1898–1900), of Westboro. He was a member of the Legislature, and during that time he was the author of the law establishing the Board of Registration in Medicine and was for many years secretary of that board. The third was Dr. George B. Francis (1902–1904), of Worcester, a Civil War surgeon. It was his steadfast demand that opened the doors of the Massachusetts Medical Society to women. The fourth was Dr. Walter P. Bowers (1912–1914) of Clinton, at one time secre-

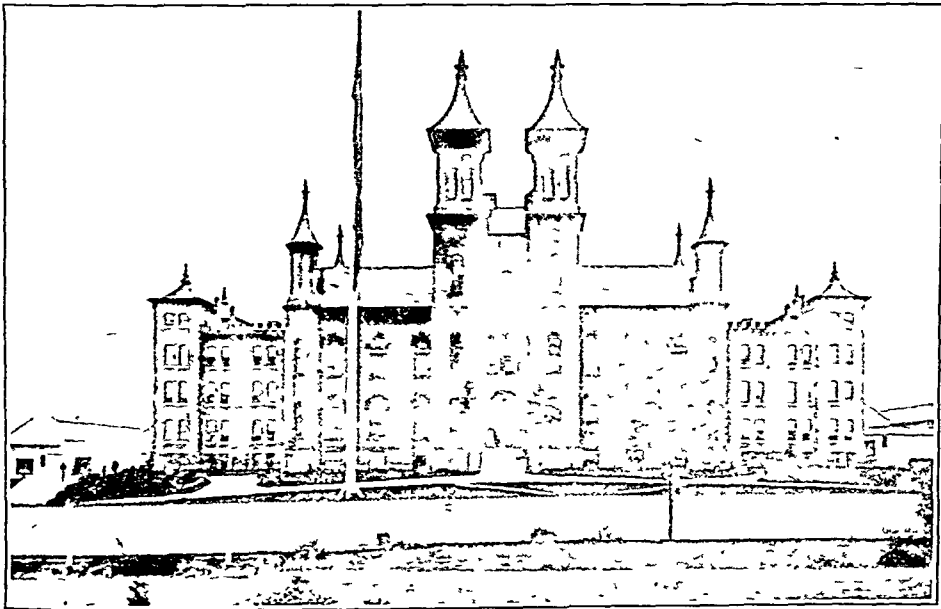


FIGURE 6. The Dale General Hospital.

in his oration before the society, quoted Dr. William Osler as stating:

There are two factors in the progress of medicine, one the skeptical spirit fostered by Paris, Vienna and Boston physicians and second, and above all, the valuable lessons of homeopathy, the infinitesimals of which certainly would do no harm and quite as certainly do no good. A new school of practitioners has arisen which cares nothing for homeopathy and less for so called allopathy. It seeks to study rationally and scientifically the action of drugs, old and new.

Thus has passed into history a controversy that was vigorous while it lasted. I prophesy that at some time whatever is of merit in any of the methods of therapy not now approved by the society will eventually be accepted by the medical profession.

Worcester District Medical Society has furnished the Massachusetts Medical Society with five of its presidents. The first of these was Dr. Thomas H. Gage (1886–1888), father of the late Dr. Homer Gage. He was the author of many medical papers, one of which on typhoid fever was epoch-making. He was a prominent churchman, was on the staff of the Worcester City Hospital, and was active in

tary of the State Board of Registration in Medicine. When the *Boston Medical and Surgical Journal* was taken over by the Massachusetts Medical Society, Dr. Bowers was the first editor-in-chief. No words can express the debt that the whole profession owes to him for the magnificent job that he did. The fifth was Dr. Samuel B. Woodward (1916–1919). He is a surgeon, the author of many surgical papers and a historian *par excellence*.

The opportunity must not be missed of reminding the society of the debt that it owes those who have furthered its aspirations for a "better city and a more enlightened profession," as Daniel Waldo wrote in his will.

Mr. Waldo was the first of these. Born in Boston, he came to Worcester at the age of nineteen, lived in his father's home at Lincoln Square and died in his stately residence on Main Street, at the present site of Mechanics Hall. He was a churchman, merchant, successful business man, importer and philanthropist. Mr. Harrison Bliss (Fig. 8), another benefactor, was at one time coachman for Dr.



Oliver Fisk, the first secretary of the society. He was a merchant, railroad president, city alderman and representative in the General Court.

Dr. Charles Wilder (Fig. 9), of Leominster, at one time president of the society, fathered a movement to build a county hospital in Worcester. Dr. Leonard Wheeler, first superintendent of the Worcester City Hospital, a gynecologist and president of the Board of Trustees of Memorial Hospital, wrote a famous paper on the Waldo, Wilder and Bliss Fund. He spent many hours on the problems of the Worcester Medical Library. Dr. Donald

Delahanty, a former president and a councilor for many years, was noted for his sympathy for the underdog. No one ever called on him in vain for help.

Dr. Samuel B. Woodward is one of the few members who have occupied all the offices in the gift of the society, having served as secretary, treasurer, president and councilor, as well as president of the Massachusetts Medical Society. He has been noted for his interest in the welfare of the city, and for years was president of the Worcester County Institution for Savings, the Taxpayers



FIGURE 7. *The American Temperance House.*

Adams, a captain in the United States Army in World War I, a surgeon at the Memorial Hospital, died in the flower of his work. To Dr. Edgar A. Fisher, a retiring man with unusual surgical and organizing ability, the success of the Hahnemann Hospital is in a considerable measure due. Dr. Michael Fallon, former president of the society, was a member of the State Board of Registration in Medicine, a councilor of the Massachusetts Medical Society for many years and the author of innumerable papers on surgery. He was for many years surgeon-in-chief and president of the staff of St. Vincent Hospital, and was an outstanding Catholic layman. Dr. Homer Gage, a former president of the society, famous son of a famous father, was successful in business as well as in surgery, a rare combination. He had plans for the future of the society that have never matured. These plans, made in 1904, are our goal today. Dr. William

Association and the Society for the Prevention of Cruelty to Children.

In Worcester County a pioneer work in industrial medicine has been done. Dr. W. Irving Clark, since 1911 head of the medical service at the Norton Company, and Dr. Theodore L. Story, since 1925 medical director of the American Optical Company, have blazed new trails in the care of thousands of industrial employees. Finally, Dr. James C. McCann, president of the Blue Shield, was largely responsible for the creation of that organization.

There are many more interesting epochs a satisfactory reporting of which space does not permit. Chief among these is the story of the contribution that this district has made to the war effort, from 1812 down to the present time.

Santayana has written, "He who does not remember history has to repeat it." It is hoped that by refreshing our minds from time to time concerning the past we can not only avoid the mistakes but be stimulated to find the answer to our unsolved

medical problems. Such an organization as ours has proved to be, together with similar societies all over the country, has the future of medicine in its hands.

Such progress made under a free system proves that if we are alert to take the initiative we can direct the changes that are on the way and preserve to our country and its people the best in medical practice.

In conclusion let me enumerate some of the notable direct or indirect contributions that Worcester County has made to medicine.

Here Dorothy Dix of Worcester taught the world compassion for the insane, and here was built the first state-controlled hospital for these unfortunates. From Oxford came Clara Barton of the Red Cross and Dr. Elliott P. Joslin, with his contributions to the treatment of diabetes. It was Charlton that gave Dr. William Morton, discoverer of surgical anesthesia, to the world. In Rutland the first state hospital for tuberculosis was built.

The society has been directly responsible for many activities that have or will spread their influence over the county, state and Nation. It was among the first to raise the standards of medical education. It forced the Massachusetts Medical Society to open its doors to statewide membership

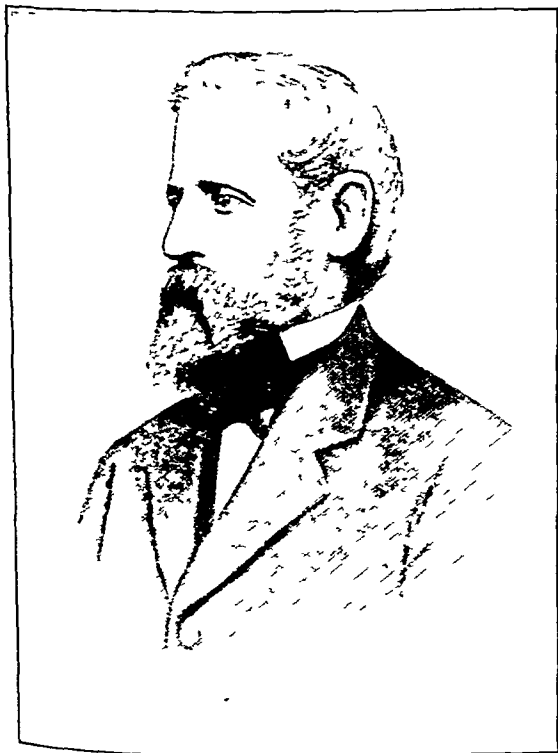


FIGURE 8 Harrison Bliss

Under its leadership, Worcester was one of the first municipalities to establish a laboratory for the diagnosis of diphtheria and tuberculosis. It organized a medical milk commission that pointed

the way to combat the terrible infant mortality during the summer months. It has overcome the menace from diphtheria. It publishes a medical



FIGURE 9 Dr. Charles W. Wilder, of Leominster.

bulletin, the first of its kind in Massachusetts. Finally it established a blood bank that is supplying both civilian and army needs

I am indebted to Mr Matthew Carrigan for the illustrations

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## THE DIFFERENTIATION OF BRONCHIOGENIC CARCINOMA AND PULMONARY TUBERCULOSIS

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**B**ECAUSE of the many clinical and roentgenologic similarities of bronchiogenic carcinoma and pulmonary tuberculosis, their differentiation may present certain diagnostic difficulties. Among

examination. An approximately equal number of cases were seen in the Diagnostic Clinic of the hospital, and the majority were referred for consultation with a thoracic surgeon. Since these patients

TABLE 1. *Summary of Proved Cases of Bronchiogenic Carcinoma.*

CASE No.	SEX	AGE yr.	SIDE AFFECTED	PERIOD IN HOSPITAL mo.	No. OF NEGATIVE SPUTUMS	COUGH	SYMPTOMS EXPECTO- RATION	HEMO- RHAGE	PAIN	DULLNESS	SIGNS RALES	ALTERED BREATH SOUNDS
1	M	40	L	5	34	+	+	0	0	+	+	+
2	M	55	R	9	29	+	+	0	+	+	0	+
3	M	66	R	7	29	+	+	+	0	+	+	+
4	M	67	R	2	4	+	+	+	0	+	+	+
5	M	51	R	3	30	+	+	+	+	+	+	+
6	M	51	L	2	15	+	+	+	+	+	+	+
7	M	61	L	1	18	+	+	+	+	+	0	+
8	M	47	R	2	15	+	+	0	+	+	0	+
9	M	57	R	1	6	+	+	0	+	+	+	+
10	M	56	R	2	17	+	+	+	0	+	+	+
11	M	63	R	½	3	+	+	+	0	+	+	+
12	M	68	R	¼	4	+	+	0	0	+	0	+

Overholt's<sup>1</sup> cases of primary cancer of the lung, there were 40 patients who were treated for pulmonary tuberculosis because of an originally erroneous diagnosis. Similarly, Moersch and Tinney<sup>2</sup> reported that in their series of 448 patients with proved bronchiogenic carcinoma, 13 spent several months in tuberculosis sanatoriums before the correct diagnosis was established. It was therefore believed that an analysis of cases of bronchiogenic carcinoma admitted to a tuberculosis hospital might shed additional light on this perplexing diagnostic problem.

Twelve such cases were found during the last ten years; they are summarized in Table 1. All were proved either by bronchoscopy or by post-mortem

were never admitted to the sanatorium, they are excluded from this study. Excluded, too, are all metastatic malignant growths and unconfirmed primary tumors. Two patients (Cases 4 and 11) who had both cancer and tuberculosis have been included.

Although these cases form too small a group for statistical analysis, they nevertheless bring out certain diagnostic points that are especially deserving of consideration.

### *Sex*

All the patients were men. Although bronchiogenic carcinoma does occur in women, it is preponderantly a male disease. In Overholt's<sup>1</sup> series, the ratio of men to women was 3.5:1.0. At the Mayo

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†Assistant physician, Norfolk County Hospital.

Clinic<sup>2</sup> this disease was found to occur nearly five times as frequently in males as in females. According to King,<sup>3</sup> 80 per cent of the cases occur in males.

### Age

The patients were between forty and sixty-eight years old at the time of their admission to the sanatorium. Although the disease may occur at any age, most cases are found between the fourth and sixth decades of life. Eighty per cent of Moersch and Tinney's<sup>2</sup> patients were more than forty years of

of these symptoms may occur in almost any combination both in bronchiogenic carcinoma and in chronic infectious diseases of the lungs. Hemoptysis may or may not be present. Pain may be entirely absent, or it may be exceedingly severe if the pleura, nerves or thoracic cage is involved by extension or metastases. All the patients in this series had a productive cough, but neither the character of the cough nor the gross appearance of the sputum was distinguishable from that found in many other pulmonary disorders.

TABLE 1. Summary of Proved Cases of Bronchiogenic Carcinoma (Continued).

Case No.	X-RAY FINDINGS			DIAGNOSIS CONFIRMED		COMMENT
	INFILTRATION	ATELECTASIS	CAVITATION	BRONCHOSCOPY	AUTOPSY	
1	+	0	+	0	+	This case was diagnosed as lung abscess. Thoracotomy and thoracoplasty were performed. The patient left the hospital at his own request, and died 20 days later at another hospital.
2	0	+	0	+	0	Bronchiogenic carcinoma was suspected on admission. The patient was bronchoscoped 29 days later. Metastatic cervical lymph nodes were discovered 12 days after bronchoscopy.
3	+	0	0	0	+	The patient was too ill for bronchoscopy. There was almost constant hemorrhage.
4	+	0	+	0	+	On admission there was a metastatic nodule on the anterior abdominal wall. Two sputum specimens were positive for tuberculosis. Autopsy confirmed both tuberculosis and cancer.
5	+	0	+	0	+	Destruction of ribs was noted by x-ray 1 month after admission. Metastases were found on post-mortem examination.
6	0	+	0	+	+	Malignancy was suspected on admission. Bronchoscopy was performed 31 days later. The patient died while awaiting transfer to a cancer hospital.
7	0	+	0	+	0	A bronchogram was taken 8 days after admission. A diagnosis of carcinoma was made clinically and by x-ray. Bronchoscopy was performed 1 month after admission.
8	0	+	+	0	+	The diagnosis of bronchiogenic carcinoma was made on admission. The patient was very ill; also had bronchiectasis.
9	0	+	0	+	0	Carcinoma of the bronchus was suspected on admission. Bronchoscopy, 21 days later, showed carcinoma in the right main-stem bronchus.
10	0	0	+	+	0	The patient was admitted for observation. Bronchoscopy was performed 1 month later. Infiltration of the trachea was seen, and mediastinal metastases were suspected.
11	+	0	+	0	+	The patient had tuberculosis of the right hand. Both pulmonary tuberculosis and bronchiogenic carcinoma were found at autopsy.
12	0	+	0	+	0	The patient was admitted for observation. Bronchoscopy, 1 day after admission, disclosed bronchiogenic carcinoma, with probable metastases.

age, and the highest incidence of the disease was in the sixth decade. The average age of Overholt's patients was fifty-five years.

### Side Affected

In 9 of these 12 cases the disease was in the right bronchial tree. According to Betts,<sup>4</sup> 31 of his 46 patients with so-called "central tumors" had right-sided involvement. Moersch and Tinney<sup>2</sup> found the disease twice as often on the right side as on the left.

### Symptoms

Bronchiogenic carcinoma presents no characteristic syndrome. This point cannot be overemphasized. Of the complaints most frequently elicited — cough, expectoration, hemorrhage and pain — all or any

The absence of pathognomonic symptoms in carcinoma of the lung has been stressed by Fetter,<sup>5</sup> Overholt<sup>1</sup> and others. Of the group of cases reported by Moersch and Tinney,<sup>2</sup> 5 per cent had, indeed, no symptoms referable to the thorax.

### Signs

The physical findings in the thoracic examination depend primarily on the size and situation of the tumor. The signs are therefore exceedingly variable, and this point has also been stressed by other writers. In the present series, dullness of some degree and alterations in breath sounds were noted in every case. Rales, often apical, were detected in 8 cases.

### X-Ray Diagnosis

The x-ray diagnosis of bronchiogenic carcinoma has recently been discussed in detail by Holmes<sup>6</sup> and Scatchard.<sup>7</sup> Overholt<sup>1</sup> has also included in his paper excellent reproductions of roentgenograms that illustrate how closely this disease may simulate pulmonary tuberculosis. Any combination of the roentgenologic findings characterized as infiltration, atelectasis or cavitation may be present. Half the cases in the present series had cavitation on their admission x-ray films.

In regard to x-ray diagnosis, Moersch and Tinney<sup>2</sup> wisely point out, "It is also important to remember that a negative roentgenogram does not definitely rule out the presence of carcinoma." If symptoms are suggestive and persistent, a negative roentgenogram should not deter one from further diagnostic studies.

### Bronchoscopy

Betts,<sup>4</sup> in a thorough discussion of the subject, has called bronchoscopy "the most important method of diagnosis in primary carcinoma of the lung." To be of value from a therapeutic standpoint, however, bronchoscopy must be performed early in the course of the disease. Usually the progress of bronchiogenic carcinoma is rapid, its duration being measured in months. The delay between the time the disease is first suspected and the time of bronchoscopy—or some other definitive diagnostic study—should be counted in days, not in weeks or months.

In half these cases the diagnosis was made by bronchoscopy, and the interval from admission to bronchoscopy varied from one day to one month. Two patients (Cases 3 and 8) were too ill for bronchoscopic examination; two other (Cases 4 and 5) had evident metastases. In 1 case (Case 1), seen in 1934 and not bronchoscoped, the diagnosis was missed clinically and made only at post-mortem examination.

### DISCUSSION

Patients with bronchiogenic carcinoma are occasionally admitted to a sanatorium either for observation for tuberculosis or because a definite diagnosis of tuberculosis has already been made. This is not surprising since, clinically, lung cancer may closely resemble tuberculosis. For this reason reliance must be placed on other diagnostic aids, such

as x-ray examination, bronchoscopy and exploratory thoracotomy. Since the x-ray film itself may also be misleading, bronchoscopic examination is of the utmost importance.

Bronchiogenic carcinoma must be promptly differentiated from tuberculosis, since time and rest never cure a malignant growth. Waiting six weeks or longer for results of animal inoculation tests or cultures of sputum may rob the patient of his chance of surgical cure.

An early diagnosis of bronchiogenic carcinoma can be made only if the disease is suspected and considered in the differential diagnosis. The possibility of cancer must be given special consideration if the patient is a man between forty and sixty years of age. In all cases in which thoracic symptoms are present, x-ray examination of the chest should be made immediately. If, on the basis of physical and x-ray examination, the disease cannot be differentiated from pulmonary tuberculosis and a few specimens of sputum are negative, bronchoscopy should be performed without further delay. Inspection of the bronchi, if the patient's general condition admits it, yields valuable information that may determine not only the diagnosis but also how the case is to be managed. This is as true of pulmonary tuberculosis as it is of bronchiogenic carcinoma, since the presence or absence of endobronchial tuberculosis may alter plans for collapse therapy. Hence, in either disease much may be gained by prompt bronchoscopic examination.

### SUMMARY

Twelve proved cases of patients with bronchiogenic carcinoma who were admitted to a tuberculosis hospital are presented. The clinical and roentgenologic similarities between carcinoma and tuberculosis of the lung are pointed out, and the diagnostic role of bronchoscopy is emphasized.

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## CLINICAL NOTE

## THERMAL BURNS IN DIABETES MELLITUS\*

HOWARD F. ROOT, M.D.†

BOSTON

THE recent report of Taylor, Levenson and Adams<sup>1</sup> emphasizes the marked hyperglycemia found in nondiabetic patients suffering severe thermal burns that involve 2 to 75 per cent of the body surface. Death occurred in 14 of their 35 cases. It is instructive to compare the metabolic changes when serious burns occur in diabetic patients in whom there is a known deficiency in insulin. For this reason, the following cases are reported to illustrate the effects of burns from hot water and from the sun's rays.

CASE 1 (4541). A 66-year-old housewife had diabetes of 7 years' duration. A leg had been amputated for gangrene on February 12, 1925, and the other leg on August 29, 1930. Although insulin had been used for a brief period at the times of operation, the diabetes was of the typically mild degree often associated with gangrene. She had therefore not regularly taken insulin, and the urine was sugar-free with diet alone. The fasting blood-sugar level had varied from 110 mg. to 210 mg. per 100 cc.

On June 11, 1931, while the patient was sitting in a wheel chair washing dishes, boiling water was spilled on her arm and back. Vomiting followed for 3 days. On June 15, she entered the Deaconess Hospital with a second-degree burn on the right arm and a large eschar on the left buttock, the site of the worst burn. She was prostrated, and although not unconscious was in severe acidosis. The blood-sugar level was 480 mg. per 100 cc., and the nonprotein nitrogen 47 mg. The carbon dioxide combining power of the venous blood was 19 vol. per cent, and rose to 27 vol. in 10 hours with 55 units of insulin.

The patient received 195 units of insulin in the first 2 days. On the 10th day, the blood-sugar level was 80 mg., and the nonprotein nitrogen 33 mg., and only 30 units of insulin was required. The urine still showed much albumin. The patient was at times irrational. At first the burns showed no evidence of serious sepsis but this later developed and she died on the 19th day.

CASE 2 (3376). A 35-year-old clerk had diabetes of 15 years' duration when he returned in 1938 for a second period of observation. In 1923 his diabetes was so mild that he required only dietary treatment for the urine to be sugar-free.

In May, 1937, he had a severe sunburn on the shoulders and back; the skin became infected, with the formation of multiple carbuncles. Presumably as a result of bacteremia, he developed phlebitis and osteomyelitis of the right leg, which necessitated a mid-thigh amputation in December, 1937. In this same month, prostatic and paranephric ab-

scesses were found, and the paranephric abscess was drained in January, 1938.

On admission to the New England Deaconess Hospital on March 3, 1938, an inguinal abscess was present, which was drained. The patient still had marked pyuria. The white-cell count was 30,000. The urine contained 1.8 per cent sugar, and the fasting blood sugar was 150 mg. per 100 cc. He was given daily doses of 10 units of crystalline and 40 units of protamine zinc insulin. Recovery was uneventful, and with the exception of a recurring abscess in the inguinal region in September, 1938, from which recovery occurred, he has done reasonably well following a diabetic diet and taking insulin as indicated.

*Comment.* The instructive feature in his case is the fact that during the period when he suffered severe sunburn and carbuncles developed, his diet was not weighed or measured and the urine was not sugar-free. The failure to control the diabetes may well have been an important factor encouraging the spread of infection, which ultimately led to an amputation of the leg, paranephric abscess and prostatic abscess.

Among the factors contributing to the increased blood sugar in the nondiabetic patients of Taylor, Levenson and Adams, increased glycogenolysis in the liver was mentioned. Another possible source of the extra blood sugar was considered to be gluconeogenesis from protein, since it has been shown that after thermal burns there is an early increase in protein metabolism. It is possible to add one other factor in discussing the causes of the change in the blood-sugar level, namely, the part played by the skin itself.<sup>2</sup> The skin normally contains much glycogen and some glucose. In diabetic patients with poor control, the normal glycogen stores are greatly reduced but the glucose is increased. This is also true with severe infections involving diabetic patients. When the blood-sugar level is high, it is possible for as much as 20 or 25 gm. of glucose to be present in the skin, and therefore if large areas of the skin are injured, liberation of glucose from the skin may contribute a material increase in blood sugar. In the cases of Taylor, Levenson and Adams, the administration of 25 gm. of glucose intramuscularly was followed by evidence of its utilization within two hours. In nondiabetic patients endogenous insulin is available, but in diabetic patients the lack of normal insulin reserve might result in quite different changes in the blood and tissue chemistry.

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## MEDICAL PROGRESS

### HEMATOLOGY (Concluded)

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#### ANEMIA DUE TO BONE-MARROW DISTURBANCES

Anemia due to a disturbance in the bone marrow is usually normochromic (normal color index) and normocytic (normal cell volume and normal cell diameter) because what red cells are produced by the more or less incapacitated marrow are normal from the standpoints of hemoglobin content and cell size. Leukopenia and thrombocytopenia are usually associated phenomena; in other words, there is a *pancytopenia*.

The presence of pancytopenia — anemia, leukopenia, granulocytopenia and thrombocytopenia — should at once lead to the suspicion that a condition involving the bone marrow is present. In general, the diagnostic possibilities are as follows: hypoplasia or aplasia of the marrow, as a rule due to chemicals, at times of idiopathic nature and occasionally associated with myxedema or nephritis; replacement of the marrow by abnormal cells, as in leukemia, lymphosarcoma, reticulosis, Gaucher's disease and fibrosis; so-called "maturation arrest," as seen in liver-extract deficiency; and diminished delivery, usually due to hypersplenism. In the last, although the marrow is normal, in fact hypercellular, the peripheral blood contains fewer red cells, white cells, and platelets than normal. Many of these cases are associated with outspoken splenomegaly. In some, the spleen, although not enlarged, is hyperactive and thus results in an undue inhibitory effect on the bone marrow. This indicates a hormonal relation between the spleen and the bone marrow.

These cases — except those due to pernicious anemia — are almost always refractory to therapy with liver extract, iron and so forth. Bomford and Rhoads<sup>18</sup> have for this reason grouped them all together in the single designation "refractory anemia," hardly a scientific term for such diverse bone-marrow pictures. My own feeling is that a serious attempt should be made in these cases to establish, so far as possible, an etiologic or at least a pathologic diagnosis. Chronic nephritis and myxedema should be ruled out by appropriate measures. The question of a more or less occult hemolytic process should be gone into by studies of the blood bilirubin, of the output of bile pigments, particularly in the feces, and of the reticulocyte level. But the central point in diagnosis is the sternal-marrow biopsy. A preliminary puncture is performed. If good flecks of marrow are obtained, giving a clear-cut picture in the stained smears, no further testing

of the marrow is required. If, however, the material aspirated is minimal in amount and contains few marrow cells, a trephine biopsy should be carried out. It is by no means necessary to remove — as is so often done — a large section of sternum through a 5-cm. or 7-cm. incision. An incision 1 or 2 cm. in length is entirely satisfactory with the use of a trephine with a head 5 to 7 mm. in diameter.

A series of excellent articles on the subject — even though the condition is, unfortunately, referred to as "refractory anemia" — is that by Davidson, Davis and Innes.<sup>19</sup> These studies are characterized by careful marrow examinations and by classification of the various cases as anemias with hypocellular, normoblastic marrows, those with cellular marrows and so forth. In the group characterized by hypocellular, normoblastic sternal marrows, 4 were secondary to chemical exposure but the remaining 12 were idiopathic. Of these 16 cases, 9 were progressive and fatal within the period of a few months. In the cases with a hypercellular megaloblastic marrow, the response to the persistent use of liver extract, although slow, was nevertheless satisfactory, and for this reason, one must seriously consider that these cases were examples of the relatively refractory type of pernicious anemia that Israëls and Wilkinson<sup>6</sup> have called "achrestic anemia." To put these cases under the nondescript term "refractory anemia" makes the whole thing rather confusing and again illustrates the value of classifying a given case of anemia on the basis of cell size, and of probable etiologic mechanisms. In a more recent paper, Davis and Davidson<sup>21</sup> point to the value of the oral administration of proteolyzed liver in a number of cases of rather atypically refractory pernicious anemia in which injections of liver extract had proved ineffective. One wonders in these cases whether the injectable liver extract was really of a high degree of potency.

Of 89 personally studied cases showing pancytopenia,<sup>21</sup> the largest group — 28 cases, or 31.4 per cent — was made up of examples of aleukemic leukemia. In these, the marrow showed an extreme degree of leukocytic hyperplasia, with the presence of many primitive leukocytes, either of the lymphoid, myeloid or monocytic variety. Thirteen cases were in a closely related category, that is, Hodgkin's disease, lymphosarcoma or multiple myeloma (plasmacytoma). Thus in 89 cases with pancytopenia, the fundamental cause of this symptom complex in almost half the cases was a proliferative disease of one of the three white cell-forming

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tissues. Pancytopenia is thus an ominous portent of these grave disorders.

Widespread fibrosis of the marrow may occur either secondarily to such conditions as leukemia, lymphosarcoma and metastatic carcinoma or, more frequently, following protracted polycythemia vera. At times it is associated with marble bone or Albers-Schönberg disease and may then be called "osteopetrosis." Rosenthal and Erf<sup>22</sup> describe 1 such case, together with 17 cases of myelofibrosis secondary to various causes. These cases, which have been described under a veritable welter of names, including leukoerythroblastic anemia, osteosclerotic leukemia, nonleukemic myelosis, leukanemia and agnogenic myeloid metaplasia, have as their distinguishing features the following: anemia and well-marked splenomegaly; bone changes consisting of irregular osteoporosis and osteosclerosis, principally in the femurs; anemia, leukocytosis or leukopenia and thrombopenia; and nucleated red cells and myelocytes, which are present in fair to considerable numbers. The presence of these early red and white cells in association with a progressive anemia bespeaks either an unusually vigorous attempt at blood formation or a rather bizarre and uninhibited type of nonproductive hematopoiesis. This is probably associated with the concomitant myeloid metaplasia of the spleen, which occurs secondarily to the initial bone-marrow fibrosis. Blood formation in the spleen is not an unnatural condition, since it probably represents a reversion to embryonic hematopoiesis; nevertheless, it lacks the normal regulatory influence that the spleen itself usually exerts on the bone marrow. This gives rise to an abnormal type of blood picture, characterized by an excess of normoblasts and myelocytes.

These cases are often difficult if not impossible to differentiate from those of chronic myelogenous leukemia with a subleukemic picture, that is, one in which the leukocyte count falls between 8000 and 20,000. In fact, some of the cases that Jackson, Parker and Lemon<sup>23</sup> have called "agnogenic myeloid metaplasia," that is, myeloid metaplasia arising *sui generis*, may in reality be examples of chronic myelogenous leukemia. That fibrosis of marrow may occur in chronic leukemia has been shown in a careful study by Churg and Wachstein,<sup>24</sup> who, in 97 cases of myeloid leukemia, found 6 showing myelofibrosis. Osteosclerosis is only rarely, if at all, associated with true leukemia. I have recently, however, seen a case that fulfilled all the criteria of myeloid metaplasia of the spleen secondary to myelofibrosis, and with the extensive bone changes of osteosclerosis, in which there were a striking regression in the size of the spleen and a striking improvement in the hemoglobin and erythrocyte values following x-radiation over the spleen. X-ray therapy and splenectomy have been said to be contraindicated because the spleen might be the only available source of hematopoiesis. A trial of

x-ray therapy in relatively small doses directed over the spleen seems to be indicated in doubtful cases.

In cases showing pancytopenia and a large spleen, and in which the marrow shows erythroblastic hyperplasia without evidence of leukemia, particularly if some evidences of increased hemolysis are present, one should at least consider the possibility of hypersplenism. Splenectomy in some of these cases has been dramatically successful, not only in raising the red-cell count to normal but also in bringing the low leukocyte and platelet counts to normal values. These cases are closely related to the syndromes of "splenic neutropenia,"<sup>25</sup> acquired hemolytic anemia and idiopathic thrombopenic purpura. The incidence of these cases should materially increase as their possibility is more frequently considered.

#### ANEMIAS DUE TO EXCESSIVE LOSS OF BLOOD

##### *Hemorrhagic Anemia*

Many cases treated routinely for months or even years with liver extract, iron and vitamin B complex are found — often too late — to be examples of chronic hemorrhagic anemia, usually secondary to bleeding from the gastrointestinal tract. With a little attention to a few morphologic details in the blood and with more frequent examinations of the stools for occult blood, these cases could doubtless be diagnosed more frequently.

Although the anemia in these cases is usually hypochromic, with color indices in the vicinity of 0.5, I have seen occasional cases with normochromic anemia, particularly when the bleeding was brisk. The white-cell count is usually low (4000 to 6000), but the granulocytes are usually slightly elevated. Stippling may be present. The platelets are usually moderately or greatly increased. The hypochromic anemia indicates a hemoglobin deficiency for the normally developing normoblasts; in association with reticulocytosis and increased platelets, indicating a hyperactive bone marrow, there is a definite likelihood of chronic hemorrhage.

Careful search for cause of the anemia should be instituted. Stool examinations for occult blood and exceedingly careful x-ray examination of the gastrointestinal tract are in order. Possibilities are diaphragmatic hernia, bleeding peptic ulcer, carcinoma of the stomach, carcinoma of the cecum or colon, Meckel's diverticulum, terminal ileitis with hemorrhage and even the lowly hemorrhoid. Lesions of the small bowel are often missed in hurried x-ray examinations, and for this reason, careful fluoroscopy with the spot film technic is invaluable.

##### *Hemolytic Syndromes*

*Mechanisms.* Little is known of the mechanisms of normal blood destruction. The mature non-nucleated red cell, after many trips about the



circulation, probably wears out and is then converted into a denatured protein, bilirubin and iron. Is the spleen truly the graveyard of the normal red cell or does it simply cause the red cells to swell as they stagnate there for variable periods? Do agents of various types — the lysolecithin of Bergenhem and Fahreus, immune hemolysins or agglutinins and various metabolic products — bring about gradual hemolysis? There is at present no answer to these questions.

Since 1940, Johnson and Freeman<sup>26</sup> have been concerned with the hemolytic action of chyle and its possible relation to normal blood destruction. After a fat meal, they state that the circulating red cells become exposed to a sufficiently high concentration of hemolytic material to cause an increase in blood destruction. This was demonstrated by exposing normal red cells to normal and lipemic serums and by observing the degree of hemolysis in both. Lipemic serums, which were obtained from persons who had taken a large amount of cream or corn oil, were slightly, although distinctly, hemolytic. Normally, however, the red cell is protected from an undue concentration of lipemic plasma by several mechanisms, including chiefly the high dilution of the hemolytic chyle that occurs with the large volume of blood in the subclavian vein and heart. Although this mechanism, as postulated by Freeman and Johnson, may well be one factor, a likelier one is probably the purely mechanical action involved in the squeezing and buffeting about which the red cell develops within the capillaries. This factor of mechanical fragility, which was investigated by Miller and myself<sup>27</sup> a few years ago, has more recently been studied by Shen, Castle and Fleming.<sup>28</sup> When normal red cells are shaken in a test tube or other container with glass beads for a given length of time, for example, three hours, a small amount of hemolysis takes place, which varies from 1 to 3 per cent. The mechanical fragility is greatly increased in the presence of an agglutinating agent (see below), which presumably still further injures the rather tough red-cell membrane. One must concede that the mechanisms of normal hemolysis are but little known and must await further elucidation.

In the field of abnormal or increased hemolysis, a number of different mechanisms may operate to destroy the red cell. One may list these as follows: bacterial agents, notably the hemolytic streptococcus; parasites, notably that of malaria and the bartonella of Oroya fever; chemicals, including the sulfonamide drugs and phenylhydrazine; immune hemolysins; agglutinins, cold and warm, usually of the immune-body type; certain physical factors, such as extreme heat and cold; unknown factors; and hypersplenism.

Bacterial agents, parasites and chemicals appear to attack the red cell directly. Hemolysins, as Dameshek and Miller<sup>27</sup> have shown, may be simple

or complex. The simple ones hemolyze the red cell directly, whereas those which are complex require the mediation of complement. Thus, with the immune hemolysin that occurs in certain cases of acute hemolytic anemia, the amboceptor has a sensitizing or agglutinating or membrane-injuring role, whereas actual hemolysis is brought about by complement. In other types of hemolytic anemia, the presence of a hemolysin may be noticeable only by the behavior of the red cell. Thus, the small, thick red cell, the spherocyte, which is fragile in hypotonic solutions of sodium chlorides, has probably been already injured by a hemolysin that cannot be detected by any means at present at one's command. The red cell of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria, which is abnormally fragile to dilute acid and also to heat, is probably abnormal because it has been acted on by a hemolysin, which itself cannot be detected. In paroxysmal cold hemoglobinuria, a well-defined hemolysin can be demonstrated, as first described many years ago by Donath and Landsteiner. This hemolysin requires so-called "sensitization" with cold, then warmth and finally the presence of complement. The chemical nature of hemolysins is almost a completely untouched field.

Agglutinins, by causing red cells to mass together, probably injure the red-cell membrane, as can be readily shown by exposing a red-cell suspension to varying concentrations of agglutinin and then shaking them in a mechanical shaker. The effect of shaking on agglutinated red cells is probably similar to the buffeting that these cells receive in a highly active circulation. In any event, the mechanical fragility of agglutinated red cells is greatly increased over normal (up to 80 per cent in a three-hour period). This is evident in transfusion reactions associated with incompatible blood. The extreme hemolysis, with hemoglobinuria and acute hemolytic anemia, that ensues is due to agglutination, with its injurious effect on the red-cell membranes, and the mechanical activity of an actively moving circulation. This type of agglutinative-hemolytic reaction is also seen in acute hemolytic anemia of the newborn (erythroblastosis fetalis) and in certain cases associated with the presence in the blood of an unusually high concentration of cold hemagglutinins.

The red cell may also be injured by a variety of physical agents, including heat, cold and various light rays. Undue heat, as in a thermal burn, by directly injuring the red cells in superficial capillaries may bring about their quick rupture and thus cause hemoglobinuria or their slower degradation by way of the spherocyte. This is another link in the concept that the spherocyte is a red cell that has been injured by some type of hemolytic agent and has therefore assumed an abnormal, unusually spherical form. This renders the cell unusually vulnerable to hemolysis by either splenic or other mechanisms.

Hypersplenism, in which an undue or abnormal activity of the spleen is postulated, is becoming increasingly evident as a cause of hemolytic anemia. The enlarged spleen of many conditions — portal hypertension, splenic-vein thrombosis, Hodgkin's disease and certain other conditions — may somehow develop an unusual degree of hemolytic activity. These cases are usually accompanied by leukopenia and thrombopenia, both of which are probably due to hypersplenic inhibition, rather than to unusual phagocytosis by splenic cells.

There are probably many other factors that injure the red cells and result in various degrees and types of hemolytic anemia. Hereditary factors involving hemoglobin metabolism and the structure of the red cell, as in Mediterranean target-oval-cell syndromes and in sickle-cell disease, and obscure factors, such as the hemolytic anemia symptomatic of Hodgkin's disease, Boeck's sarcoid and dermoid cyst, are among these totally unknown causes of increased blood destruction. A consideration of the etiologic factors may be distinctly worth while in working out the possible mechanism in a given case of hemolytic anemia and in making the ultimate decision regarding the value of splenectomy as a therapeutic procedure.

*Differential red-cell fragility.* Red-cell fragility has for many years been associated with the reaction of red cells to hypotonic salt solutions. This test serves only to discriminate between cells showing varying degrees of thickness, the range of hemolysis in a given case indicating the limits of the "thickness population" of the red cells. Normally, some begin to hemolyze in a 0.45 per cent solution of sodium chloride but all become hemolyzed at a 0.25 per cent concentration. Thick red cells — spherocytes — begin to hemolyze at concentrations close to that of normal saline solution, and thin red cells — leptocytes or target cells — are at times incompletely hemolyzed even in solutions containing as little as 0.04 per cent of sodium chloride. An amusing, although sound, article from Honolulu on erythrocyte fragility is that by Fennel,<sup>29</sup> who recommends a simple one-tube "screen test" for determining whether or not abnormal hypotonic fragility is present. A 0.38 per cent solution of sodium chloride is employed, and the degree of hemolysis is measured with the photoelectric colorimeter. If any increase in the normal degree of hemolysis is present, a second or serial dilution test is carried out. The author concludes, "At least, try the one tube of 0.38 per cent saline in conjunction with your routine hematology, and see if you don't get interested."

One should always realize that whatever a red cell shows in its reaction to hypotonicity does not necessarily indicate its reaction within the circulation, where everything is always isotonic. There may, then, be other ways of measuring red-cell vulnerability or fragility.

The question of acid hemolysis or fragility has already been mentioned. In one disease, and apparently in only one, as Ham<sup>30</sup> and others have pointed out, the red cell is unusually vulnerable to dilute acids. A presumptive test may be made with carbon dioxide gas, and the complete test with various types of dilute acids, with and without complement.

The matter of mechanical fragility has also been alluded to. It may be worth while to introduce this method as a more or less routine measure in the study of hemolytic anemias. Mechanical fragility is increased in the presence of warm and cold hemagglutinins (when testing for the latter, the serum must be kept cold) and to some extent in such conditions as sickle-cell and other hemolytic anemias.

Heat fragility has recently been introduced by Hegglin and Maier.<sup>31</sup> This is a simple test in which a tube of clotted blood is placed in an incubator at 37°C. for three to twenty-four hours. Apparently in only one disease, again paroxysmal nocturnal hemoglobinuria, are sufficient red cells hemolyzed with simple incubation to result in hemolysis readily visible to the naked eye. The precaution must be used of taking the blood with a dry syringe and under as little stasis as possible.

One may thus study the resistance of the red cells in a given case of hemolytic disease by at least these four methods and arrive at a more or less etiologic diagnosis. Doubtless, other methods may be used, as Dameshek and Singer<sup>32</sup> suggested some years ago, including resistance to saponin, lecithin, lysolecithin and so forth. The concept of differential fragility serves to indicate that when the red cell is injured by different substances it reacts differently.

*Clinical features.* As pointed out in previous reviews, three types of *hereditary hemolytic syndromes* may be discriminated: familial spherocytosis (congenital or familial hemolytic anemia or jaundice); Mediterranean target-oval-cell disease (Cooley's anemia, thalassemia, Mediterranean anemia or familial leptocytosis); and sickle-cell anemia. Of these, familial spherocytosis is by far the best known. Mediterranean target-oval-cell disease has been known for some years as a severe, fatal condition. The milder types have only recently been studied (Wintrobe et al.,<sup>22</sup> Dameshek<sup>31</sup> and Smith<sup>26</sup>). These observers have all pointed out the numerous gradations in the types of cases — from the most fatal form, Cooley's anemia, down to the extremely mild cases, in which abnormalities can be demonstrated only by careful hematologic studies. The severest cases show marked anemia, increased hemolysis, splenomegaly, significant bone changes and the presence of numerous nucleated red cells in the circulating blood. Moderately severe cases present moderate anemia, splenomegaly, slight icterus and minimal bone changes. Mild cases show absolutely nothing on physical examination and only slight

hypochromic anemia or erythrocytosis in the blood counts. All types, severe, moderate and mild, show target and oval red cells in varying concentrations and increased resistance of the red cells to hypotonic salt solutions. The red cells are unusually thin, apparently because of a disturbance in hemoglobin synthesis, with the formation of normal-sized cells lacking sufficient hemoglobin for the amount of cytoplasm that is present. Iron therapy is totally ineffective, and hemoglobin values remain surprisingly constant.

These cases are apparently transmitted by a Mendelian dominant mechanism. A careful study of them from the standpoint of the morphology of the blood was made by Valentine and Neel.<sup>36</sup> The mild cases are apparently transmitted by a heterozygous gene, but the severe cases are transmitted through two parents, both bearing this gene. This confirms my own studies,<sup>34</sup> which showed that both parents of patients with severe cases (Cooley's anemia) showed mild target-oval-cell abnormalities. Valentine and Neel point out that this is one of the few diseases in which carriers can be discriminated by careful laboratory studies. These syndromes deserve increasing attention, since they are undoubtedly frequent among Italians and not infrequent among Greeks, Syrians and Portuguese. Anemia, jaundice, splenomegaly, peculiar bone changes and stippling of the red cells occurring in one of these racial groups should always make one consider the possibility of a target-oval-cell syndrome.

More attention is also being paid to sickle-cell disease, which in many respects resembles target-oval-cell disease rather strikingly, and may in fact be related to it. In sickle-cell disease, as in the Mediterranean syndromes, a central feature is the presence of thin, hypotonically resistant, target cells. Hemolysis and splenomegaly are features of the severe cases, and there is no response to the administration of iron, despite the hypochromic character of the anemia. The carriers of the disease may well be those with the sickling trait, who number about 7 per cent of the Negroes in this country. Sickle-cell disease, although almost exclusively limited to those of African origin (colored), also occurs to some extent in Italians and occasionally in Portuguese — apparently without any colored admixture. The highly abnormal sickled cell may be related to the elongated, elliptical cell of the Mediterranean disease.

An interesting study of the occurrence of sickle-cell disease in the black Carib Indian had been made by McGavack and German.<sup>37</sup> The black Caribs are not truly Indians but natives of Honduras who have preserved for centuries the purity of their original racial African stock. Twenty-four (8 per cent) of the 300 persons studied showed the sickling phenomenon. None had apparently had sickle-cell

disease, and sickle-cell anemia as such had never been recorded in the local hospital.

Murphy and Shapiro<sup>38</sup> describe a new technic for demonstrating the sickling trait. By this method the process of sickling can be readily studied from the stage of the normal flexible red cell to the stage of sickling when flexibility is lost and the cell appears "as fixed and rigid as a crystal of ice as it moves about and abuts against cells and fixed objects." These and other observations led Murphy and Shapiro to conclude that the dissociation of combined hemoglobin bears a causal relation to the phenomenon of sickling. Because of its rigidity within the circulation, the sickled cell may be unusually vulnerable to mechanical trauma (mechanical fragility).

Winsor and Burch<sup>39</sup> showed that the sedimentation rate in sickle-cell anemia may be used as a diagnostic measure. By oxygenating sickle-cell blood the sedimentation rate increases, and by adding carbon dioxide to the blood the rate decreases. Instead of adding carbon dioxide to the blood, one may study the sedimentation rate of blood taken with and without stasis by means of a tourniquet applied for six minutes. The lability of the sedimentation rate with respect to oxygen and carbon dioxide and the relation of the different rates to each other are said by the authors to comprise a "diagnostic parameter." If the difference between the two sedimentation rates is greater than 20 mm. per hour, the patient has sickle-cell anemia.

Bauer and Fisher<sup>40</sup> describe a nonanemic variety of sickle-cell disease. All Negro patients should be routinely tested for sickle-cell disease to avoid such erroneous diagnoses as rheumatic fever, rheumatic heart disease, polyarthritis and cerebral disease. The authors report 6 cases in which the pathologist diagnosed the condition post mortem; in 5 of these the clinician had not even suspected the condition. Brugsch and Gill<sup>41</sup> report 4 cases of sickle-cell anemia in which the diagnosis was obscured by the presence of polyarthritis and heart murmurs simulating rheumatic fever. Italians, too, may have symptoms simulating various conditions but which in reality are due to sickle-cell disease. Thus Canby, Carpenter and Ellmore<sup>42</sup> report a case in which an apparently acute surgical condition of the abdomen in a youth of pure Sicilian stock was due to multiple infarctions of the spleen. Splenectomy was performed, and later sickle-cell anemia was discovered. Reinhard, Moore, Dubach and Wade<sup>43</sup> describe the results of a careful study of the effects of high concentrations of inspired oxygen in patients with sickle-cell anemia. Although a decrease in the degree of intravascular sickling of the red cells occurred, there was no consistent detectable change in the rate of hemolysis. In fact, erythrocytogenesis was depressed by the oxygen therapy, both the reticulocytes and the red cells being decreased; when

oxygen was discontinued, a striking increase in reticulocytes occurred.

A good review article on the *acquired hemolytic syndromes* is that by Davis.<sup>44</sup> Acute hemolytic anemia following the administration of sulfadiazine is often accompanied by the presence in the blood serum of a cold hemagglutinin. This has been commented on, among others, by Layne and Schem<sup>45</sup> and by myself.<sup>46</sup> The exact relation of the cold hemagglutinin to the drug and to the hemolytic anemia is obscure. Its presence in high titer may lead to a false interpretation of "incompatibility" in testing the patient's serum with prospective donor's red cells prior to transfusion. This may readily be obviated by performing the cross-match according to Landsteiner's test-tube method at incubator temperature. The blood should be warm when administered; if bank blood is used, it should be allowed to warm at room temperature for two or three hours. Stats<sup>47</sup> studied 2 cases in which extremely high titers of cold hemagglutinin were present, demonstrating the importance of mechanical trauma as a cause of hemolysis in agglutinated red cells. This is in line with the previous work of Dameshek and Miller<sup>27</sup> showing the injurious effect of agglutinin on the red-cell membrane and the importance of mechanical trauma as a cause of hemolysis whenever a hemagglutinin in sufficiently high titer is present. This is presumably true not only in patients with a cold hemagglutinin but also in transfusion accidents due to incorrect cross-matching and to the presence of an anti-Rh agglutinin (Rh-factor reaction). The red cells are injured when they become agglutinated, and being present in agglutinated masses, they are vulnerable to the constant buffeting about in an active circulation. Intravascular hemolysis then takes place, with resultant hemoglobinemia and hemoglobinuria. Masses of acid hematin are usually precipitated in the renal tubules, and nephropathy follows. A case of chronic hemolytic anemia with autoagglutination and hyperglobulinemia is reported by Kracke and Hoffman.<sup>48</sup> A similar case was recently studied by Katz and myself.<sup>49</sup> Hyperglobulinemia was also present and was presumably due to the exceedingly high titer of cold hemagglutinin, which was 1:500,000. Intravascular agglutination could be readily demonstrated by microscopic examination of the capillaries at the nail bed and in the cornea. Hemoglobinemia occurred when a whole arm was immersed in iced water.

Acute hemolytic anemia of the newborn (erythroblastosis fetalis) has now been firmly established as due to a reaction between the Rh antibody (anti-Rh agglutinin) and the Rh factor or agglutigen. Levine,<sup>50</sup> whose pioneer work in this field is outstanding, presents a review of the pathogenesis of the disease. In this paper, the technics of agglutination tests and their interpretation, the varieties of human anti-Rh serum, the matter of the so-called

"Hr factor" as it occurs in mothers who are Rh+, familial and racial factors and the treatment with transfusions of Rh- blood are discussed. This article will repay careful reading. Another excellent and comprehensive review is that by Potter.<sup>51</sup> Comments concerning the laboratory problems involved in Rh-factor testing are presented by Kracke and Platt.<sup>52</sup> These are often difficult. The clinician reading a report of "Rh-" or "Rh+" rarely knows the difficulties that are often encountered in the laboratory in making the decision. Too many weak serums are on the market that give false negative reactions. Until a good animal or other method is developed for preparing anti-Rh serum, these difficulties will doubtless continue. The other big problem is the possibility of developing some method for neutralizing the mother's anti-Rh agglutinin so that it cannot agglutinate the fetus's Rh+ red cells. Until this comes about, the erythroblastotic-producing mother is faced with the constant and recurring threat, with each new pregnancy, of the development in the fetus of hydramnios, acute hemolytic anemia, severe jaundice and so forth.

The *idiopathic hemolytic anemias*, unassociated with agglutinins or reactions to drugs, are of great interest. I have recently seen an increasing number in which the spleen seemed to be the central feature of the disease and the resulting hypersplenism the cause of the hemolytic anemia, the leukopenia and the thrombopenia. The mechanisms by which the spleen in these cases gives rise to increased hemolysis are quite obscure. The leukopenia and thrombopenia may be explainable by an unusual degree of inhibition of the bone marrow by an overactive spleen. Splenectomy is usually — not always — followed by a dramatic rise in the red-cell count to a normal or increased value. I<sup>53</sup> have discussed the physiologic pathology and the therapy of these cases in a recent article.

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**Correction.** In the review of medical progress "Parenteral-Fluid Therapy. I. Estimation and provision of daily maintenance requirements," by Drs. Allan M. Butler and Nathan B. Talbot, which appeared in the October 26, 1944, issue of the *Journal*, the figure "10" in Column A of Figure 3, which specifies the volume of 5 per cent amino acids, should be changed to "110."

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31101

#### PRESENTATION OF CASE

**First admission.** A fifty-four-year-old practical nurse was admitted to the hospital because of progressive muscular weakness and a skin eruption.

Five months prior to admission the patient began to feel weak, fatigued easily and perspired excessively. Her symptoms progressively increased. About two months before entry, she developed an erythematous rash on the back of the neck and around the fingernails. This gradually involved the forehead, the perinasal regions, the ears and chin, the arms and the dorsal aspects of both hands. It was associated with slight itching, and there was deep tenderness on pressure over these areas. There was no history of exposure to drugs or chemicals,

\*On leave of absence.

nor had there been any recent exposure to sunlight. About five weeks before entry she developed gradually increasing edema of both eyelids and exhaustion became so marked that she was forced to stop working. In the month before admission muscular weakness increased to the point where the act of combing the hair on dressing herself required considerable effort. Pain and stiffness at the base of the neck prevented her from holding the head erect. A sensation of a lump in the throat made swallowing difficult. Her weight fell from about 200 to 180 pounds.

The patient gave a history of intolerance for highly spiced and fried foods for many years. About ten to twelve years previously she had had severe attacks of indigestion and excruciating pain in the right upper quadrant radiating through to the back. These attacks lasted several hours and were associated with vomiting of bitter material. There was no history of jaundice or of clay-colored stools. Two months before admission she was found to have a repeatedly positive Wassermann reaction, for which she had received two injections of Mapharsen.

The patient's mother and two half uncles died of tuberculosis. One of her daughters also had tuberculosis. Her husband had a positive Wassermann reaction.

Physical examination revealed a well-developed and well-nourished woman who appeared acutely ill. There was marked periorbital edema, and some

puffiness over the hands and forearms. An irregular, symmetrical, bright erythematous eruption, sharply demarcated from the surrounding skin, was present over the forehead, perinasal area, cheeks and chin. A more diffuse, pigmented eruption was present over the neck posteriorly and on the abdomen. The hands, forearms and shoulders revealed a raised, red, papular eruption, both discrete and confluent, which was most pronounced on the extensor surfaces and around the nails. The lungs were clear, and the heart, except for a soft blowing systolic murmur over the entire precordium, was normal. Neurologic examination revealed some muscular weakness of the back, the arms and, to a lesser degree, the legs. There was no evidence of atrophy, ataxia or tremor. The gag reflex was absent on the right and practically absent on the left. All the deep tendon reflexes were present and equal. Sensory tests were normal.

The temperature was 98.8°F., the pulse 90, and the respirations 20. The blood pressure was 145 systolic, 70 diastolic.

Examination of the blood showed a red-cell count of 4,400,000, with 14.7 gm. of hemoglobin. The white-cell count ranged from 4300 to 8900, with 64 to 74 per cent neutrophils, 18 to 29 per cent lymphocytes, about 6 per cent monocytes and 1 per cent eosinophils. Examination of the urine revealed only a few white cells in the sediment. The serum non-protein nitrogen level was normal, and the protein 6 gm. per 100 cc. The van den Bergh and cephalin flocculation tests were negative. A bromsulfalein test showed 15 per cent dye retention. The Hinton and Wassermann tests were repeatedly positive. A lumbar puncture revealed clear fluid under an initial pressure equivalent to 165 mm. of water. The Wassermann test was positive, and the gold-sol curve was 0011100000. A heterophil agglutination test, skin tests with trichinella antigen and blood cultures were negative.

A roentgenogram of the chest was normal. A Graham test revealed no filling of the gall bladder with dye, and there was a 4-cm. laminated stone in the area.

Over a period of several months, the patient continued to complain of extreme muscle weakness and ran a low-grade fever, usually below 100°F. A therapeutic test with 0.5 mg. of Prostigmine produced no change in symptoms. The eruption, especially that on the face, shoulder and back, became more pronounced and dusky in color and was associated with some edema about the eyes. Numerous transfusions were given. Several infected decubitus ulcers developed on the buttocks and over the right elbow. These were treated with sulfadiazine and azochloramid packs. About five months after admission the patient began to complain of distressing gas pains and diarrhea, with four to five rather loose stools daily, on which guaiac tests were negative. At that time, examination

revealed a firm, slightly movable mass in the right upper quadrant, descending with respiration. A rectal examination revealed a small ulcer on the anterolateral wall, which was confirmed by proctoscopy. The edges were thickened and irregular, and the ulcerated area bled on slight trauma. The mucosa of the remainder of the rectum was finely granular and indurated, but no other ulcers were seen. A biopsy of the ulcerated area revealed acute inflammation.

Following this episode the patient began to improve in appearance and spirits. She received 25 mg. of testosterone propionate intramuscularly every two days, but it was noted that the tendency to the improvement antedated this treatment. A gastrointestinal series was made at the beginning of the eighth hospital month. The patient swallowed the barium mixture without difficulty. The esophagus, stomach and small intestine failed to reveal any definite variation from the normal. The gallstone previously described was still present. A barium enema revealed an area of narrowing at the rectosigmoid junction, extending for a distance of 1 cm. This was never seen to dilate more than 1.5 cm.; it did not change in appearance and revealed no areas of ulceration. No other abnormality was seen.

Following the patient's striking improvement, associated with increase in weight, well-being and ability to get about by herself, she was discharged to a nursing home at the end of the ninth month.

*Second admission* (five weeks later). A few days after her arrival at the nursing home the patient developed spells of vomiting once or twice daily, usually after meals. These were rapidly followed by loss of strength, and she lost 10 pounds in the interval. The vomitus was never black or bloody, nor was there any jaundice or fever. There was mild constipation. Four days prior to admission she developed severe, diffuse, lower abdominal pain and cramps, relieved by the passage of gas. On several occasions she passed a loose stool, together with considerable gas but no blood. The vomiting continued. On the day prior to entry she developed a fever (about 102°F.) for the first time since her discharge.

Physical examination revealed an emaciated woman in moderate distress. The skin showed dry areas of whitening and brownish pigmentation over the face, chest, back and hands. The musculature was atrophic. The lungs were clear. The abdomen was moderately protuberant and exquisitely tender, especially in the lower quadrants. Rebound tenderness was present, but there was no spasm, nor were any masses palpable. Peristalsis was greatly diminished. There was tenderness over both costovertebral angles. A pelvic examination revealed marked tenderness on manipulation of the cervix. Rectal examination showed a questionable ulceration just inside the sphincter on the anterior wall.

The temperature was 101.6°F., the pulse 100, and the respirations 20. The blood pressure was 110 systolic, 60 diastolic.

Examination of the blood revealed a red-cell count of 5,500,000, with 100 per cent hemoglobin, and a white-cell count of 11,900, with 85 per cent neutrophils, most of which were band forms. The urine was normal. The serum nonprotein nitrogen level was normal, and the protein was 6.6 gm. per 100 cc.

A roentgenogram of the abdomen revealed numerous dilated loops of small bowel, and gas was present in the stomach. X-ray examination of the chest revealed little change in the lung fields, but the heart appeared to have increased in size.

A Miller-Abbott tube was passed into the jejunum, and dextrose in water and normal saline solution were administered intravenously. Sulfadiazine was also administered, together with several transfusions. By the eighth hospital day the temperature was normal, and examination of the abdomen revealed normal peristalsis. Tenderness in the lower quadrants was reduced and she had several normal bowel movements. Hourly films of the small bowel showed slight delay in transit, seven hours being required for the barium to reach the colon. There was no definitely abnormal dilatation of the small bowel when barium was present in the loop, but on some of the films there appeared to be dilatation, mucosal irregularities and loss of pattern before the barium entered the loop.

Two days later the temperature rose to 103.2°F. She passed a stool consisting of mahogany-colored fluid with a ++ guaiac reaction, followed on the next day by a semisolid, brown, guaiac-negative stool. The abdomen was generally tender, with rebound tenderness and mild spasm. Rectal examination revealed several extremely tender shallow ulcerations just inside the anus anteriorly; they had the appearance of fistulas. A Levine tube was passed, and 400 cc. of black watery fluid, becoming thick and tarry, was aspirated. The guaiac reaction on this material was ++++. Many rales were audible over both lung bases, and the pulse was rapid. An x-ray film of the chest, taken with the portable machine, revealed linear areas of increased density in the right upper and left midlung fields. An electrocardiogram revealed low voltage in the standard leads, with flat T<sub>1</sub>, low to diphasic T<sub>2</sub>, slightly inverted T<sub>3</sub> and inverted T<sub>4</sub>; R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> measured 3, 2 and 2 mm. respectively, and S waves were absent.

The patient rapidly became comatose and died on the fourteenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. CHESTER M. JONES: My first reaction to this interesting story was that the total picture might have been due to tuberculosis. We know that the patient had gallstones, on the basis of a history of biliary colic and x-ray evidence of stone. We also

know that the patient had syphilis, on the basis of numerous positive serologic tests. Arsenical treatment for syphilis was initiated just about the time that the first skin lesions appeared, and it may be of some interest to speculate on the possible role of arsenic in causing the skin lesions. The exposure to tuberculosis in various members of the family is also of interest. Careful evaluation of the progress of symptoms, which started some months prior to the skin eruption, leads me to believe that the gallstones and the syphilis had nothing to do with the fundamental picture as it unfolded. The possible role of tuberculosis remains to be considered. The patient had a story of almost a year's duration, with marked skin changes, intermittent fever and a final elevation of temperature. Furthermore, there was a definite story of rectal ulceration, and a terminal story of that as well as the picture of peritonitis, which makes me think that she had perforated one of the rectal ulcers or one higher up in the colon. She had a rectal stricture and, in addition, a story from the very beginning of progressive muscular weakness and atrophy. The cause of the terminal hematemesis is obscure.

Is there any single diagnosis, aside from gallstones and syphilis, that covers all the facts? If we tie them all together one has to think in terms of tuberculosis, with skin lesions, with gastrointestinal lesions and possibly, because of the rales in the chest, a hematogenous spread at the last moment and a resultant miliary tuberculosis. I am not entirely happy with such an explanation. Syphilis, it seems to me, could explain this picture by stretching one's imagination to the limit. She could have had a rectal stricture due to syphilis. She had a positive spinal-fluid Wassermann reaction, but there were no signs or symptoms of syphilis of the central nervous system. She had a negative gold-sol curve, and there was no increase in the spinal-fluid cell count or protein. It is hard for me to believe that she had central-nervous-system syphilis. There is no evidence that points strongly to cardiovascular syphilis, and syphilis that would produce rectal stricture, ulcers, bleeding and peritonitis is something that I have not seen. I suppose it can occur, because anything can happen with syphilis; but it is not a logical diagnosis. What other things can cause stricture besides syphilis? We may think of it in terms of lymphogranuloma inguinale, but the remaining symptoms are not those of this disease.

If we start with the skin lesions, which I am not qualified to discuss, I should merely say that the erythematous lesions appeared rather suddenly, with muscular weakness, periorbital edema, loss of weight and gastrointestinal symptoms that for the moment we shall leave out. One has to think of lupus erythematosus disseminatus, scleroderma and dermatomyositis. These three diseases ought to be considered in view of the peripheral mani-



festations. I think possibly that each of these conditions could cause that part of the picture. No skin biopsy was taken, although she was in the hospital for nine months; at least there is no record. If it was diagnostic, it may have been omitted purposely. Skin and muscle biopsies of dermatomyositis at the proper stage of the disease, which, as I understand it, is late in the course of the disease, are distinctive and show a degenerative process. There is edema around the muscles, and subcutaneous edema, which can be demonstrated histologically as well as clinically. In scleroderma one observes edema under the skin and thickening, but not the histologic picture of muscular degeneration that is seen in dermatomyositis. In disseminated lupus, except as a wasting disease, I do not believe that one expects muscular atrophy. I am sure that the attention of an expert skin pathologist is required before one can be dogmatic about the diagnosis of disseminated lupus on a skin biopsy. I believe that periorbital edema is likelier to be present in dermatomyositis than in scleroderma or in disseminated lupus. I shall hazard the guess that if this were disseminated lupus over an entire year's period the patient should have had a more elevated temperature than she did have, although I should be glad to be corrected on that point. Muscular weakness is characteristic of dermatomyositis in a large number of patients and at times mimics myasthenia gravis. We know that the diagnosis of myasthenia gravis was considered because the patient was given Prostigmine as a therapeutic test. Five tenths of a milligram is the usual dose, is it not, Dr. Ayer?

DR. JAMES B. AYER: Yes.

DR. JONES: It produced no change, and it would be unusual for myasthenia gravis not to respond to such a dose. I think this diagnosis can be dismissed. Furthermore, the whole course of the disease is not too consistent with myasthenia gravis, although the patient did have progressive muscular weakness.

In considering scleroderma, there are one or two other things that I can add in a hesitating fashion. We do know that one observes gastrointestinal lesions in scleroderma, and as Hale<sup>1</sup> and others have shown, evidence of generalized stiffness and edema and a fibrotic condition involving the esophagus, with a lack of normal peristaltic activity. Ulcerative lesions have not been described in the gastrointestinal tract in scleroderma to the best of my knowledge. Whether dermatomyositis can be associated with similar lesions, I do not know. It is a queer disease, and I am sure that we do not know all its manifestations. Scleroderma is also a queer disease, about which we know very little. Disseminated lupus, to my knowledge, is not associated with ulcerative gastrointestinal lesions. That very fact, if I am going to stick to one diagnosis, rules

out lupus, along with other things that I have mentioned.

Tuberculosis with queer skin manifestations can certainly answer this diagnostic problem. Ulcerations of the gastrointestinal tract are not too infrequent in tuberculosis and can produce, after healing, a stricture of the rectum. It is hard for me to make a single diagnosis that covers all the findings, but what I can do is to indicate the possibilities that occur to me. The terminal event, I think, was the final episode of a prolonged disease, with perforation of an ulcer and peritonitis; on the other hand, the terminal cause of death may have been a coronary accident. The linear shadows in the chest suggest pulmonary emboli, which may have occurred late in the illness. In dermatomyositis one often observes electrocardiographic changes suggesting involvement of the myocardium, as well as that of the voluntary muscles. I am not at all certain that these changes are diagnostic, but I believe they have been reported. Excessive sweating is one of the interesting phenomena supposed to take place in dermatomyositis.

That is as far as I can go without making rash statements that have no meaning whatever. I shall therefore say that this patient had gallstones and probably cholecystitis, both of which had nothing to do with the rest of the picture. I believe that she had syphilis; I am sure that such a diagnosis does not explain the whole setup, and as near as I can come to tying it in is to say that the rectal fistula might have been syphilitic in origin. Beyond that I believe that she had one of the three conditions that I have mentioned — dermatomyositis, scleroderma or disseminated lupus erythematosus. Of the three, I shall put dermatomyositis first, admitting that I know nothing about the gastrointestinal lesions in that disease. I shall choose scleroderma as a close second, because I know that digestive-tract lesions have been found on several occasions in this curious disease. It may well be that there was tuberculosis as an added factor, which would help to explain the gastrointestinal symptoms, but it had nothing to do with what originally brought her to the hospital.

I am a little intrigued by the statement, or by the fact, if it is a fact, that some of the skin lesions appeared after two doses of Mapharsen. It is possible that inadequate antisyphilitic treatment was associated with syphilitic skin lesions that can behave this way when latent syphilis is treated inadequately. I cannot explain the skin lesions on the basis of reactivation of the syphilis or on the basis of syphilis itself, except the papular lesions, which were rather odd.

I should like to see the x-ray films. I do not believe that she had tuberculosis of the stomach, which is exceedingly rare and mimics cancer.



DR. MILFORD D. SCHULZ: This is certainly a curious small-bowel pattern (Fig. 1). There is some edema of the wall. The picture is much like what Dr. Hale has described in scleroderma.<sup>1</sup> None of the bowel loops seem to be fixed in relation to one another for any period of time, as one would expect to see if the patient had had tuberculous peritonitis.<sup>2</sup>

DR. JONES: One might add that that fits in with the story that she was depleted from apparent partial intestinal obstruction. It took nine hours for barium to go through the intestinal tract, which implies that the motor activity of the small bowel

DR. JONES: Was the balloon put in to hold the barium in the colon in order to take the picture?

DR. SCHULZ: I think that it was.

DR. JONES: In that case it suggests an atonic anal sphincter, a condition often associated with dermatomyositis or scleroderma.

DR. SCHULZ: Or syphilis.

DR. JONES: What about the linear shadows in the chest film? Do they suggest infarction?

DR. SCHULZ: Here are two that suggest scars of old infarcts; such a lesion was apparently not present on the films taken eleven months previously.



FIGURE 1. Roentgenogram Showing the Distribution of Barium in the Small Bowel Six Hours after Administration.

*Note the evidence of slow transport and of mucosal swelling.*

was interfered with by some intrinsic nerve disorder or by an infiltrative process.

DR. SCHULZ: The fluoroscopist could have better described the findings, but the barium-filled esophagus looks wide and stiff — a lead-pipe appearance. It may have contracted later, but it had not at the moment when these films were made.

DR. JONES: Have you a picture that shows the rectal ulceration and stricture? That worried me more than anything else.

DR. SCHULZ: Here is a film after a barium enema. The ulcer seems to be in the sigmoid. The rectum appears normal. Of course there is a balloon in it, and the normal rectum does not balloon out to that size without protest.

DR. JONES: You can see no evidence of recent infarcts?

DR. MAURICE FREMONT-SMITH: One argument for scleroderma is the tenderness over the areas of edema. I do not believe that Dr. Jones brought that out. Furthermore, an argument against lupus is the absence of albumin and red cells in the urine. I also do not know whether intestinal symptoms go with the strange disease called dermatomyositis.

DR. BENJAMIN CASTLEMAN: Dr. Lever, will you comment, from the dermatologic point of view, on the differences between these two diseases.

DR. WALTER F. LEVER: From the standpoint of the dermatologist, the diagnosis in this case lay between lupus erythematosus and dermatomyositis,

rather than between scleroderma and dermatomyositis. For a diagnosis of scleroderma, one expects a certain amount of boardlike induration of the skin and subcutaneous tissue, which was absent in this patient. The cutaneous lesions were suggestive of lupus erythematosus in that there were erythema and atrophy, but the same type of lesions can be found in dermatomyositis. In favor of dermatomyositis was the presence of tenderness over the involved areas of skin, and also the muscular tenderness. In scleroderma, muscular atrophy may be just as severe as in dermatomyositis, but usually it is not combined with tenderness of the muscles. So, from the dermatologic point of view, the diagnosis was dermatomyositis.

#### CLINICAL DIAGNOSES

Dermatomyositis, generalized.

Generalized peritonitis.

Acute pancreatitis?

Mesenteric thrombosis?

#### DR. JONES'S DIAGNOSES

Dermatomyositis or scleroderma.

Peritonitis, following perforation of the colon.

Old pulmonary infarcts.

Cholelithiasis.

Syphilis.

#### ANATOMICAL DIAGNOSES

Dermatomyositis.

Ulcers of esophagus, jejunum and rectum, with perforation of several jejunal ulcers.

Fibrous and myxomatous intimal proliferation of intestinal arteries, with thromboses.

Abscess, pelvic, right.

Peritonitis, acute, fibrinopurulent.

Bronchopneumonia.

Lipid pneumonia.

Arteriosclerosis, generalized.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: As Dr. Jones inferred, a biopsy had been done at the time of the first admission and the diagnosis of dermatomyositis was established. The autopsy also showed what Dr. Jones predicted. This woman had a perforation of the intestine, with acute purulent generalized peritonitis. Numerous sections of striated muscle throughout the body showed severe degeneration. In some areas there was no cellular infiltration, but in others it was marked. There is no question about the diagnosis of dermatomyositis.

The intestinal tract was unusual, and as could be seen from the roentgenogram of the gastrointestinal series, the small intestine, especially the jejunum, was markedly edematous. Throughout the jejunum were numerous ulcers, some tiny and others measuring up to 1 cm. in diameter. A few of these had perforated and had produced peritonitis. There were also ulcers in the rectum that were similar to those seen in the jejunum, but we

did not find any evidence of stricture. There were no ulcers in the duodenum or other parts of the colon, but the entire bowel was markedly edematous, thick and brawny. Microscopic examination showed

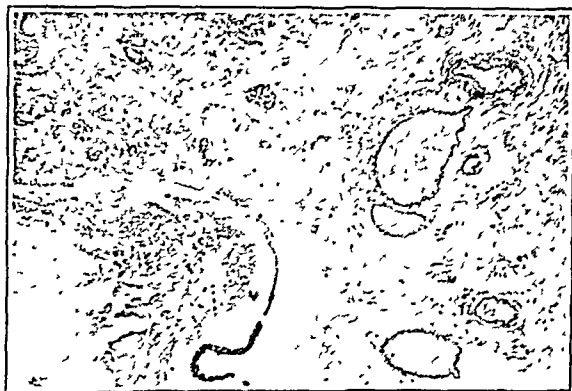


FIGURE 2. Photomicrograph of One of the Ulcers of the Small Intestine.

*Note the extensive arterial disease in the submucosa.*

that most of the edema was in the submucosa. The bases of the ulcers were covered with fibrin and an extensive lymphocytic and polymorphonuclear leukocytic infiltration (Fig. 2). In the edematous



FIGURE 3. Photomicrograph at a Higher Magnification of One of the Vessels in the Submucosa.

*Note the marked intimal proliferation with luminal narrowing.*

submucosa beneath the ulcers, and also in regions that were not ulcerated, the large vessels showed pronounced fibrous and myxomatous intimal proliferation with marked luminal narrowing (Fig. 3). Some of the vessels were completely occluded, and

others contained recent or organized thrombi. The ulcers were almost certainly the result of the vascular disease. An occasional vessel showed organized thrombosis with recanalization (Fig. 4). These vascular lesions were found only in the intestines. We hunted throughout the sections of the various other organs but were unable to find anything similar to the lesions found in the intestine. They duplicated the changes seen by Dr. Gall in the kidneys of a case of dermatomyositis that we had several years ago.<sup>3</sup> In that case, the myxomatous intimal lesion was found only in the kidneys. The kidney sections in this case were perfectly normal, except for evidence of mild arteriosclerosis, certainly



FIGURE 4. Photomicrograph of Another Vessel.  
Note the thrombosis with recanalization.

nothing that simulated the vascular changes that were found in the intestines.

DR. JONES: What did you find in the heart?

DR. CASTLEMAN: Nothing. There was no degeneration. We have recently gone over all our cases of dermatomyositis and were unable to find any definite change in the heart muscle. In one case the myocardial findings were equivocal.

DR. FREMONT-SMITH: Do you call this whole disease process dermatomyositis? Is it all part of the same picture?

DR. CASTLEMAN: I believe so.

DR. MARIAN ROPES: Clinically, I have noted intestinal symptoms in at least two other cases with long periods of severe diarrhea. Such cases usually do not have guaiac-positive stools and do not reach this picture by x-ray.

DR. JONES: I should like to ask if gastrointestinal lesions have been described in dermatomyositis. That is an important point.

DR. LEVER: They have been described in a few cases. In Potain's<sup>4</sup> case, the autopsy revealed multiple visceral infarcts. In the case reported by Karelitz and Welt,<sup>5</sup> diffuse enterocolitis with intestinal ulceration was encountered. The arteries of the small intestines showed marked edema and round-cell infiltration between the fibers of the muscular layer. The case cited by Schuermann<sup>6</sup> presented hemorrhages into the mucosa of the stomach, with early necroses, as well as erosions in the lymphatic tissue of the lower small bowel. Vascular lesions were absent.

DR. CASTLEMAN: Because of the dermatomyositis, these patients are prone to have trouble in swallowing, as this patient had. The administration of mineral oil should be avoided, lest some of it pass down the larynx and into the lungs. This patient must have been taking mineral oil for some time, because we found a great many foci of lipid pneumonia throughout all lobes, especially the lower ones.

DR. JONES: Do you want to comment on the difference between this and scleroderma? Are the lesions of scleroderma like this?

DR. CASTLEMAN: I do not recall a case of scleroderma with bowel lesions. I have just seen a report that describes marked atrophy of the musculature of the gastrointestinal tract but no vascular lesions similar to those in this case of dermatomyositis.<sup>7</sup>

DR. JONES: Certainly the number of patients with scleroderma who have gastrointestinal symptoms and x-ray signs is much larger than that of those with dermatomyositis.

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#### CASE 31102

##### PRESENTATION OF CASE

A seventy-seven-year-old widow entered the hospital because of marked dyspnea, abdominal distention and tenderness in the right upper quadrant.

Nine years before admission she had a subtotal thyroidectomy for nontoxic goiter, 140 gm. of tissue

having been removed. The pathological report was "hypertrophied." After recovery she lived at a home for aged women, where her activities were limited. Five years before admission she received some medical attention for "gall-bladder trouble" and "a heart condition." She had at that time only shortness of breath and could not take digitalis because this caused vomiting. She spent nine weeks in bed and was well thereafter. Three months before admission she began having pain in the right upper quadrant, which came on only after lying in bed. This pain lasted up to two hours, varied in severity and had no relation to food or exertion. Long-standing constipation became accentuated and required an additional laxative tablet each day. Four days before admission she entered the Emergency Ward because of painful migratory arthritis involving both feet and the right hand. Physical examination and x-ray study at that time were consistent with rheumatoid arthritis. She was discharged to the Out Patient Department. One day before admission, distention of the abdomen began after an unsuccessful enema had been given and the patient's dyspnea increased. Repeated enemas resulted in several loose movements, without relief of the distention or the dyspnea. On the day of admission she had had two episodes of vomiting.

Physical examination revealed a dyspneic woman in moderate discomfort but without pain. The lips, ears and mucous membranes were cyanotic. The heart was not enlarged, and the sounds were normal. The neck veins were slightly distended and pulsating. Bilateral crackling basal rales were heard, and in the same areas there was increased dullness to percussion. There was no peripheral edema. The abdomen was markedly distended and tympanic. Peristalsis was diminished. There was tenderness in the right upper quadrant. No abdominal splinting or masses were noted. Rectal examination was negative. The rectum was filled with soft, tan feces, which were guaiac negative.

The rectal temperature was 100°F., the pulse 84, and the respirations 20. The blood pressure was 168 systolic, 80 diastolic.

Examination of the blood revealed a red-cell count of 3,800,000, with 10.5 gm. of hemoglobin, and a white-cell count of 16,000, with 91 per cent neutrophils. The urine was acid and had a specific gravity of 1.016, with a +++ test for albumin and occasional white cells and casts. The Bence-Jones protein was negative. The serum nonprotein nitrogen was 42 mg. per 100 cc., and the total protein 5.8 gm., with an albumin-globulin ratio of 1.1. The carbon dioxide and chloride levels were normal. The phosphorus was 1.4 mg. per 100 cc., and the alkaline phosphatase 10.6 Bodansky units.

X-ray films of the chest showed mottled areas of increased density scattered throughout the lungs.

The vascular shadows were increased in size. The heart was prominent in the region of the left ventricle and the aorta tortuous. Films of the abdomen showed considerable gas in the small and large bowel, neither of which appeared to be dilated. There was a laminated gallstone in the region of the gall bladder. No abnormal soft-tissue masses were seen. An electrocardiogram showed normal rhythm at a rate of 75, a PR interval of 0.16 second, a flat T<sub>1</sub>, upright T<sub>2</sub> and T<sub>3</sub>, and a biphasic T<sub>4</sub>, with a sagging ST<sub>4</sub>. The patient was digitalized with Cedilanid and was given sulfadiazine.

On the second hospital day the patient was considerably improved and was no longer orthopneic, dyspneic or cyanotic; the lungs had cleared but a few patches of fine rales persisted at both bases posteriorly. The abdominal distention was diminished, and two masses in the right upper quadrant could be felt 5 to 7 cm. below the costal margin. These were nontender and descended with inspiration; they were thought to be due to a coarsely irregular liver edge. The sulfadiazine level was maintained at about 10 mg. per 100 cc., with an intake of about 1250 cc. and an output of about 1000 cc.

At 12:50 a.m. on the fifth hospital day she had an episode of steady precordial pain with gradual onset. Moderately severe orthopnea, with a respiratory rate of 40, lasted about twenty minutes. Repeated electrocardiograms showed inverted T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub>, and a sagging of all ST segments. X-ray films of the chest on the same day showed that the mottled areas of increased density previously described had cleared considerably. Only moderate congestion of the vessels was noted, and no infarcts were seen in a posteroanterior view. The nocturnal dyspnea recurred during the succeeding two nights. There was no increase in the pulmonary rales.

A bromsulfalein test on the fifth hospital day, using 5 mg. of the dye per kilogram of body weight, showed 80 per cent retention in forty-five minutes. A van den Bergh test was normal. An aspiration biopsy of the liver showed no abnormality. The cephalin flocculation test was + in forty-eight hours. A barium enema was negative.

The white-cell count rose steadily and reached 31,400 on the eleventh hospital day, with 75 per cent neutrophils, 5 per cent lymphocytes, 4 per cent eosinophils and 16 per cent large monocytes. A low-grade fever (99 to 100°F.) and anemia persisted. The stools were brown and formed. The urine persisted in showing a +++ to ++++ test for albumin and a specific gravity of 1.006 to 1.020.

On the twelfth day the patient suddenly had an attack of acute pulmonary edema, for which she was treated with tourniquets, morphine, Cedilanid and, finally, venesection. She rallied but developed peripheral edema. She became incontinent, with slowly increasing depression and unresponsiveness, and died on the twenty-third hospital day.

## DIFFERENTIAL DIAGNOSIS

DR. REED HARWOOD: Whatever else we are dealing with in this case it is evident that the patient had congestive heart failure. I think that two questions should be considered—first, the type of heart disease that was responsible for the failure and, second, whether any further disease contributed to her death.

Nine years before admission she had a subtotal thyroidectomy. This raises the question of myxedema. If she did have myxedema it is not evident from the record.

Four days before admission she came to the Emergency Ward, complaining of painful migratory arthritis. It is unusual but not impossible to see acute rheumatic fever in a person of this age; I have seen it in persons of fifty years. One would expect, however, to find an increased PR interval in the electrocardiogram and to have more statements about her joints after she was admitted to the hospital.

The low-grade fever and the anemia suggest a subacute bacterial endocarditis, but I consider that as remote. She was an old woman who had a moderate hypertension. The x-ray films showed some enlargement of the left ventricle, and I think it is likely that she had hypertensive heart disease. At her age it is reasonable to expect that she had sclerosis of the coronary arteries. I suggest that she had a combination of hypertensive and arteriosclerotic heart disease.

The initial electrocardiogram was not strikingly abnormal, and I am interested to see if the changes that took place were consistent with an infarct. She was given digitalis, and we therefore expect to find sagging of the ST segments. I cannot say with complete confidence, however, that these tracings are consistent with an infarct. But since, following the attack of precordial pain, there was a definite change in  $CF_1$ , it seems extremely likely that she had a myocardial infarct.

In answer to the first question, that is, the type of heart disease responsible for failure, I believe that she had hypertensive and arteriosclerotic heart disease, with a small myocardial infarction while she was in the hospital.

Did she have anything else that contributed to her death? She had abdominal pain and constipation shortly before admission; she was found to have a secondary anemia and a persistent ++++ test for albumin, without striking abnormalities in the urinary sediment. The attending physicians evidently considered the possibility of multiple myeloma because of the marked albuminuria and anemia, but the test for Bence-Jones protein was negative and the serum protein was not markedly increased. I do not believe that this entirely rules out multiple myeloma, but at least the evidence is against it. It was found that she had a phosphorus

of 1.4 mg. per 100 cc. and an alkaline phosphatase of 10.6 Bodansky units, both of which are abnormal figures. The only condition that I know of in which the phosphorus is reduced to such a low figure is hyperparathyroidism, but that may be ignorance on my part. If at post-mortem examination an adenoma of the parathyroid gland was found, I should be willing to give the opinion now that it did not contribute to her death. I am inclined to think that she did not have an adenoma, because there is so little evidence to go with it. The alkaline phosphatase was definitely increased, which suggests some disease of the bone in which the osteoblastic activity is increased. Once again one thinks of hyperparathyroidism, Paget's disease or some type of malignant disease involving the bone.

Another finding is the presence of two masses in the right upper quadrant. For lack of a better explanation I decided that she had a liver that was probably engorged from early right-sided failure of the heart and a chronically inflamed gall bladder. Both masses were rather low in the abdomen, at least four fingerbreadths below the costal margin. She might conceivably have had a diseased kidney on that side.

We next come to the consideration of disease of the liver, about which there are many contradictory data. Evidently the attending physicians thought that she had liver disease. They did a bromsulfalein test on the day that she had acute left ventricular failure and found that she had 80 per cent retention. At the same time a van den Bergh test was normal. A biopsy of the liver was normal, and a cephalin flocculation test was not definitely abnormal. The serum protein level and the albumin-globulin ratio were normal. With all this negative evidence I am going to disregard the bromsulfalein test or at least not give it undue importance. I do not know what happens to the bromsulfalein test in cases of congestive failure, but it is at least possible that during acute congestive failure more of the dye would be retained.

Finally, there was a peculiar reaction of the bone marrow, which had produced a leukocytosis by the twelfth hospital day. I should like to know about some of the other white-cell counts and differentials during the preceding interval.

DR. BENJAMIN CASTLEMAN: On admission, the white-cell count was 16,000; subsequently, it was 13,000, 18,000, 23,000 and 31,000; on the tenth day it was 32,000, and then 18,000 and 32,000. In the differential counts the neutrophils ranged from 91 to 74 per cent, and then from 71 to 77 per cent.

DR. HARWOOD: When did the monocytosis appear?

DR. CASTLEMAN: On the tenth day, there were 5 small lymphocytes and 3 monocytes; on the fifteenth day, 5 small lymphocytes, 6 large lymphocytes and 3 monocytes; three days later, 4 large lymphocytes, 9 small lymphocytes and 8 monocytes, with 2 myelocytes.

DR. WYMAN RICHARDSON: There were numerous smears interpreted by different persons.

DR. JAMES A. ROTH: The monocytes were not typical. They were large mononuclear cells, which I could not classify. They stained light blue.

DR. HARWOOD: I should like to ask Dr. Schulz if there is anything in the chest plate to suggest any disease other than congestive failure.

DR. MILFORD SCHULZ: The pulmonary markings are prominent. They do not look just like the prominent markings that are seen with lymphatic spread of a tumor. There is not much fluid in the chest. In the lateral view there is a triangular shadow in the posterior gutter that could indicate an infarct, but it is not entirely characteristic.

DR. HARWOOD: Do you want to say anything about the bones?

DR. SCHULZ: All the bones are decalcified but no more than one would expect in a person of her age. There is no evidence of cysts, and no change in the vertebral bodies. There are old arthritic changes in the hands and feet. I do not see any localized areas of destruction.

DR. HARWOOD: Is there anything suggestive of miliary tuberculosis in the lungs?

DR. SCHULZ: The picture is not consistent with that of miliary tuberculosis. Lungs that look like this are disturbing. One thinks of passive congestion, early lymphatic spread of malignant disease, pulmonary fibrosis and even miliary tuberculosis; something similar is often seen in diseases like periarteritis nodosa.

DR. HARWOOD: Do you see anything in the lungs that suggests the need for sulfadiazine? The temperature was 100°F. when the patient came in, and she had a high white-cell count. There is nothing in the record, however, to give me a clue why sulfadiazine was necessary, and this raises the question why patients have to be treated with some kind of chemical. We know that occasionally a fever subsides without their use, and I doubt that this patient needed sulfadiazine. I shall proceed, leaving the statement for what it is worth.

To go on with the discussion, I think that some other disease besides heart disease was found post mortem. I have no idea what, but the evidence points to a lesion that involved bone. I should think, first of all, of a malignant tumor with widespread metastasis, including involvement of the lungs. The original site of such a tumor I cannot determine. It may have been the thyroid gland, the gall bladder or some other intra-abdominal organ.

Another possibility is miliary tuberculosis. The evidence for this is not striking. I also thought of the possibility of some acute intra-abdominal catastrophe to explain the increasingly high white-cell counts, such as thrombosis or embolus of some vessel or perhaps perforation of the gall bladder.

I remember a patient with carcinoma of the prostate who developed a high fever and chills. I thought that he had a kidney infection, but at post-mortem examination we found that the gall bladder had ruptured into the bed of the liver, discharging a hundred or more small stones. It was an entirely unsuspected finding. In the present case, I also thought of the possibility of disease in the liver. The likeliest lesion would be a metastatic carcinoma.

DR. RICHARDSON: I did not see this patient, but I did see a blood smear taken at about the midpoint of her illness. At that time she had received sulfadiazine for some time. The picture was that of a considerable degree of leukocytosis. There was no evidence of infection from the smear. There were some peculiar cells, which might have been very immature red cells, and I thought that the whole picture might have been due to sulfonamide therapy. Sulfonamides had been stopped, however, a few days previously, but still the total white-cell count remained elevated. There was also red-cell regeneration. I wrote in my note that since the picture had continued after the stopping of sulfonamides it was quite consistent with involvement of the bone marrow, presumably by a malignant tumor that had also produced considerable anemia. There were no toxic changes such as are usually seen in uremia, nor was it hypochromic by measurement. It was a "simple anemia" but must be explained somehow.

Not knowing the answer in this case, I should say that the patient probably had malignant involvement of the bone marrow. The possibility of myeloma should be considered. Those queer cells might conceivably have been immature plasma cells.

DR. CHESTER M. JONES: I should like to take minor exception to one statement that Dr. Harwood made, namely, that an elevated phosphatase means disease of bone. That is not correct because an elevation of the phosphatase level may also occur in liver disease and may be as high or higher than that noted in involvement of bone.

DR. HARWOOD: Is that true in patients without jaundice?

DR. JONES: Yes.

Dr. Harwood was entirely right in stating that the elevation of the bromsulfalein retention could be explained by congestive failure. No doubt one could observe dye retention, positive cephalin flocculation and Takata Ara tests and at least some change in the albumin-globulin ratio as a temporary episode occurring with congestive failure. On the other hand, 80 per cent retention in forty-five minutes is extremely high.

I do not recall this case too well, since the patient came in at a time when I was out of the hospital for a few days. I do recall, however, that we entertained the thought of metastatic cancer of the liver as a real possibility and that is why the biopsy was

done. The fact that nothing was found on aspiration biopsy is no proof against its existence. One can miss a nodule very easily.

#### CLINICAL DIAGNOSIS

Metastatic carcinoma to lungs and liver?

#### DR. HARWOOD'S DIAGNOSES

Hypertensive and arteriosclerotic heart disease, with congestive failure.

Carcinoma of gall bladder or thyroid gland, with metastases to bone marrow?

#### ANATOMICAL DIAGNOSES

Carcinoma of gall bladder, with extension into liver and with metastases to lung, liver, peritoneum and bone marrow.

Cardiac hypertrophy, hypertensive type, slight. Cholelithiasis.

Hydrothorax, slight, bilateral.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The post-mortem examination disclosed a heart weighing over 400 gm., with slight

hypertrophy of the left ventricular wall, which is consistent with a mild hypertensive heart. There was no infarction, and the coronary arteries were only slightly sclerotic. We found no real evidence of heart failure. There was about 50 cc. of fluid in both pleural cavities. The liver showed no evidence of chronic passive congestion, but it was enlarged. In the region of the gall bladder was a mass about 6 or 8 cm. in diameter that completely replaced the gall bladder and that looked like carcinoma. It extended into the liver substance for about 4 or 5 cm. In cutting through this mass we found a gallstone embedded within. Microscopic sections revealed that this was a primary carcinoma of the gall bladder. The increase in pulmonary markings was due to metastatic carcinoma.

DR. RICHARDSON: What about the bone marrow?

DR. CASTLEMAN: There were also metastases to the peritoneum and to the bone marrow.

DR. SCHULZ: Was the entire bone marrow replaced?

DR. CASTLEMAN: We have not seen enough sections to say, but the one section that I examined certainly showed extensive involvement.

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## "KEEP 'EM ALIVE IN 'FORTY-FIVE"

It has been well said that instead of trying to make ourselves happier and other people better, we should make ourselves better and other people happier. The American Red Cross, which is now conducting its annual War Fund drive, is making a great many people happier—or at least much less miserable. In so far as the Nation supports its endeavors, we shall be a better people. Immediate incentives are the mounting casualty and prisoner-of-war lists, and the enthusiastic endorsement of the Red Cross by military and naval leaders. The number of chapters in Greater Boston—twenty-two—amalgamated for the drive is the

SOMETIME sportswriter Bill Cunningham has acquired new stature as he has found new fields in which to try his strength. In the January 21 issue of the *Boston Herald* he took his fling at the stubbornly cherished belief that a diagnosis of psychoneurosis, particularly when it has been applied to a soldier, constitutes a stigma denoting mental deterioration or moral weakness.

## THE "PSYCHONEUROTIC"

most generous extent possible.

The necessity for the Red Cross is too obvious and widely known to require emphasis. General Eisenhower has said of the organization, "We simply couldn't get along without it." The Red Cross budget for 1945 represents an increase of 12.5 per cent over the previous year, so that it behooves all who can contribute to the drive to do so, and to the

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## PLYMOUTH DISTRICT

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1101 Beacon Street, Brookline  
CREEDEN, FRANKS V., 327 Boylston Street, Boston.  
Georgetown University School of Medicine, 1941.  
DEL COLLANO, MICHAEL R., Washington Street, South Easton.  
Middlesex University School of Medicine, 1936. Sponsor: George A. Moore, 167 Newbury Street, Brookton.  
SHAPIRO, HARRY, 64 Seaver Street, Stoughton.  
Middlesex University School of Medicine, 1931. Sponsor: Jacob Brenner, 8 Oliver Street, North Easton.  
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Goddard Hospital, Brockton

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ALEXANDER, WALTER J., 137 Peterboro Street, Boston.  
University of Buffalo School of Medicine, 1942.  
BLOOMFIELD, RICHARD A., Boston City Hospital, Boston.  
Harvard Medical School, 1938.  
DUSTON, CHARLES H., U. S. Marine Hospital, Cleveland, Ohio.  
Tufts College Medical School, 1938.  
FORZIATI, ANTHONY A., 35 Washington Avenue, Winthrop.  
Middlesex University School of Medicine, 1932. Sponsor: George H. Schwartz, 19 Princeton Street, East Boston.  
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College of Physicians and Surgeons, Boston, 1937.  
Sponsor: Jacob J. Abrams, 562 Shirley Street, Winthrop.  
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Boston University School of Medicine, 1942.

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New York Medical College, 1942.

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Boston University School of Medicine, 1943.

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Heights.  
Creighton University School of Medicine, 1927.

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THE EARLY DIAGNOSIS OF DISEASES OF THE CHEST\*

NORMAN J. WILSON, M.D.

BOSTON

THE early diagnosis of diseases of the chest is a matter of more importance to the physician today than at any time in the history of medicine. This is true for the following reasons. Intrathoracic abnormalities and diseases are more frequent than has ever been suspected before, as has been revealed by mass x-ray surveys in recent years. Modern diagnostic procedures make early diagnosis more easily attainable than ever before. Modern medical

early. In spite of the fact that the tools with which to work are now available, there is overwhelming evidence from mass surveys and the analysis of case histories that the early diagnosis of intrathoracic disease, as already stated, is accomplished in the minority rather than in the majority of cases. Sixty per cent of the tuberculous patients in this country who are referred to sanatoriums have far advanced

Not so long ago the physician had to rely on the history, the physical examination and inadequate bacteriologic study of the sputum to establish a diagnosis of intrathoracic disease. As is well known, diagnoses were made during this era in the vast majority of cases only when the pathologic process was in a moderately advanced or far advanced stage. In addition, the available methods of treatment were extremely limited and of questionable effectiveness. These facts led to the hopeless attitude of the medical profession and laymen alike toward these maladies. In recent years, however, great strides have been made in the diagnosis and therapy of diseases of the chest. Fluoroscopy and roentgenography have become universally available. More recently, mass surveys with miniature film taken with photofluorographic technic have brought onto the horizon the possibility of x-raying the chest of almost every man, woman and child in a given community at a cost of only a few cents per person.

Because of the physician to establish the proper diagnosis of the lung area referred for surgery before metastases or extension of the tumor has occurred. In a study of 153 patients with cancer of the lung, Overholt<sup>1</sup> discovered that in 95 cases (60 per cent), not only had an incorrect diagnosis been made, but also treatment based on it had been maintained for long periods of time. The average patient went to the doctor three months after the first symptom occurred. It required an average of three and a fourth months for the physician to request the first x-ray film of the chest. The correct diagnosis was not established until another six months had passed. Thus, definitive therapy was delayed an average of nine months from the time of the first visit and — what is more alarming — for six months after the roentgenogram had revealed the lesion. In other words, only three months of the delay was due to the patient and nine months was due to the failure of the physician to establish the proper diagnosis

A study of this problem has suggested several reasons for the delay in diagnosis. The patient frequently delays going to the physician because the incipient stage of the disease process is so frequently

\*Presented at the annual meetings of the Massachusetts Medical Society, Boston, May 24, 1944.

associated with few or no symptoms; the presenting clinical picture often suggests another diagnosis; physical examination is notoriously unreliable because of the paucity or absence of physical signs; and the application of rigid diagnostic methods is often delayed because the physician has not developed a sufficiently strong suspicion of the underlying disease.

#### MISLEADING NATURE OF CLINICAL PICTURE

The early clinical course of intrathoracic lesions is apt to be misleading because symptoms are either absent or extremely mild or masquerade as some other disease process. The important clinical fact that physicians must come to recognize more fully is that there is almost always an early asymptomatic stage, during which the process can be discovered only by routine roentgenogram of the chest. When symptoms do occur, they usually point to disease in the chest, but they are apt to be so mild that the life-threatening cause is not suspected. As a result, many of these patients are treated for bronchitis, the common cold, grippe and so forth.

The masquerading character of carcinoma of the lung has been emphasized by Alexander<sup>2</sup> and Overholt.<sup>1</sup> Just how important a factor this is can be gleaned from the fact that 60 per cent of 153 patients studied by Overholt were treated on the basis of an incorrect diagnosis. These diagnoses included tuberculosis, unresolved pneumonia, lung abscess, bronchitis, asthma, heart disease, pleurisy, metastatic cancer and arthritis. Benign lung tumor may also present a similar bizarre clinical picture.

The masquerading character of pulmonary tuberculosis has not been so well described in the literature, but during the last few years I have seen tuberculosis simulate the clinical picture of bronchiectasis, abscess, asthma, pneumonia and carcinoma, as well as other less well defined clinical pictures, such as bronchitis and virus pneumonia. Recent bronchoscopic studies have revealed that 10 per cent of patients with pulmonary tuberculosis also have involvement of the major bronchi.<sup>3</sup> As a result, stenosis is not infrequent and, like cancer, may cause all degrees of bronchial occlusion, with resulting obstructive emphysema, atelectasis and suppuration. Wheezing is a usual complaint of these patients, and they often seek advice because they believe that they have asthma. The wheezing, however, is always unilateral, and this should serve to differentiate it from true asthma.

Pleurisy, with or without effusion, spontaneous pneumothorax, persistent hoarseness or anal fistula may be the first condition of which the patient with pulmonary tuberculosis complains. All such patients should have chest roentgenograms to rule out pulmonary tuberculosis. In those with pleural effusion, the pleural fluid should be studied for tubercle bacilli by examination of a concentrated specimen, culture and guinea-pig inoculation. Be-

cause of the serious prognostic significance of pleural effusion, especially in young people, these patients should be treated as if they had parenchymal tuberculous lesions and followed routinely by frequent x-ray films of the chest. As Kallner<sup>4</sup> found, 39 per cent of patients with pleural effusion who were denied sanatorium therapy developed pulmonary tuberculosis, usually within five years, and 22 per cent of these patients died. This is in striking contrast to the good prognosis of such patients when properly treated, as reported by Trudeau.<sup>5</sup>

No attempt will be made to cover completely the symptoms associated with intrathoracic diseases, but the following points require emphasis. Almost all the diseases of the chest have an early asymptomatic stage, during which the pathologic process can be discovered only by x-raying the chest. This stage is apt to be so mild that the seriousness of the underlying lesion is overlooked. The masquerading tendency of intrathoracic disease, especially cancer and tuberculosis, has been emphasized. They may masquerade as each other, or as any of the commonplace diseases of the chest, or as an entirely foreign clinical picture, such as arthritis.

#### UNRELIABILITY OF PHYSICAL EXAMINATION

Physical examination of the chest is an essential procedure in the evaluation of any patient, especially those with diseases of the chest. Relinquishment of such procedures is not advocated, but it must be emphasized that the time has come to recognize their limitations as well as their value. As early as 1933, Sampson and Brown<sup>6</sup> reported that the staff of the Trudeau Sanatorium had concluded that moderately coarse rales at an apex were the only reliable data obtained on physical examination, and added that these were present in only 27 per cent of the minimal cases. They analyzed the occurrence of the five cardinal signs and symptoms of tuberculosis in a series of 280 cases with minimal disease. Tubercle bacilli were found in the sputum in 35 per cent, rales in 27 per cent, hemoptysis in 26 per cent, pleural effusion in 12 per cent, and x-ray evidence of pulmonary tuberculosis in more than 99 per cent. These pioneers pointed the way to the early diagnosis of pulmonary tuberculosis over a decade ago, yet in the everyday practice of the country and in the teaching of medical students methods of diagnosis are predominantly employed that cannot claim more than a 25 to 30 per cent efficiency. This partially explains why 85 to 90 per cent of patients with pulmonary tuberculosis are diagnosed only when they have reached the moderately advanced or far advanced stages.

In respect to carcinoma of the lung, physical signs are usually absent in the very early stages. Unilateral wheeze and suppression of breath sounds due to obstructive emphysema are the most frequent early signs. When bronchial obstruction is more complete, signs of atelectasis, consolidation or ab-



access may be present. It is only fair to state that physical signs are extremely unreliable and at best only suggestive in cases of pulmonary cancer.

#### VALUE OF ROUTINE FLUOROSCOPIC EXAMINATIONS

In 1927, the Metropolitan Life Insurance Company made fluoroscopic examination of the chest a routine supplement to each physical examination at its home office.<sup>7, 8</sup> This enabled the examiners to discover intrathoracic abnormalities and disease that would have been missed by physical examination and history. As a result, treatment was started in the majority of cases before physical signs or symptoms had become apparent.

Block and Tucker<sup>9</sup> recently reported to the American Trudeau Society their experiences with routine fluoroscopic examination of the chest of all patients admitted to the University of Chicago Clinic. The results of this admirable clinical study, which was applied to 15,000 cases, were remarkable. Positive findings were revealed in 3187 cases (21.3 per cent).

The incidence of tuberculosis in this group of patients was 4.2 per cent, that of clinically significant tuberculous lesions 1.4 per cent, that of tumors of the lung 0.6 per cent, that of mediastinal and diaphragmatic disease 0.6 per cent, and that of cardiovascular disease 14.4 per cent. In addition, there were other significant findings, such as pleural diseases, anomalies, skeletal disease, foreign bodies and subternal thyroid glands. The significant fact concerning the pulmonary tuberculosis discovered by this method was that two thirds of the patients had minimal lesions, one sixth moderately advanced, and one sixth far advanced lesions. This represents a reversal of the distribution of the stages of tuberculosis in patients referred from private practice to sanatoriums. On the basis of this study Block and Tucker estimate that in the fifteen years prior to the institution of routine chest fluoroscopic examination, 3000 cases of active tuberculosis were missed in their clinic in spite of careful history-taking and physical examination. They also state that in the coming year about 600,000 patients with pulmonary tuberculosis will undergo physical examination in hospitals and physicians' offices of this country without a diagnosis being established.

These data demonstrate the value of routine fluoroscopic examination of the chest as a supplement to the physical examination. They further show the inefficiency and inadequacy of the history and physical examination in apprehending intrathoracic abnormalities in the early stage of development.

#### VALUE OF ROUTINE ROENTGENOGRAMS

Stereoscopic 14-by-17-inch films remain the most ideal means of demonstrating lesions of the chest, but the prohibitive cost of this procedure, together with the demand for a cheaper and less cumbersome form of chest roentgenography for mass surveys,

has led to the development of miniature films taken by photofluorographic technique. The 35-mm. and 4-by-5-inch films are the ones in general use. Plain or stereoscopic views may be taken. Birkelo<sup>8</sup> has demonstrated that the 4-by-5-inch film can be used in mass survey work with only a 2 per cent margin of error, as compared with results obtained with the regular 14-by-17-inch film.

The utilization of this technique in mass surveys has served to demonstrate that intrathoracic abnormalities, neoplasms and infections are much more frequent than has been assumed from available clinical or autopsy data. Under the direction of Hodges,<sup>10</sup> of the University of Michigan Hospital, every patient admitted to the clinic since July 1, 1941, has had the benefit of a 35-mm. photofluorographic examination. Thorough roentgenologic study has been recommended for any patient whose miniature film reveals a significant abnormality. During the first four months of this work, 7841 patients were examined. Of these, 74.0 per cent had no abnormality, 14.1 per cent had deviations from normal not considered to be clinically significant, and 9.3 per cent had abnormalities demanding more extensive roentgenologic study. Hodges states, "Photofluorography employed to survey the chests of all patients regularly registered in hospitals and clinics can be expected to disclose signs of significant thoracic disease in 8 to 10 per cent of the patient group."

The foregoing data demonstrate conclusively that some form of roentgenologic study of the chest should be a routine procedure in the examination of every patient admitted to hospitals and institutions. Routine blood-cell counts reveal blood dyscrasias in a small fraction of 1 per cent of cases, routine urinalysis reveals diabetes in about 0.4 per cent, and routine serologic tests reveal syphilis in about 2 per cent. These routine laboratory procedures have been required for years in every good clinic and hospital. Yet, today, these same institutions are neglecting a procedure that will uncover 8 to 10 per cent significant thoracic disease. In the light of present knowledge, routine roentgenologic study of the chest is at least four times as efficient and important as any other routine procedure now in use. In addition to its value as a diagnostic aid, it serves to protect patients and the hospital personnel against the unsuspected active cases of tuberculosis that are constantly present in hospitals without any isolation technique whatsoever being applied. When either fluoroscopy or photofluorography is used, the procedure requires little time and can be done at a cost of only a few cents a patient. The additional expense can be defrayed by a minimal charge added to the laboratory fee.

#### VALUE OF SPUTUM STUDIES FOR TUBERCLE BACILLI

In every patient suspected of having tuberculosis careful sputum studies should be performed in an

attempt to confirm the diagnosis. A positive sputum, however, is not an absolute requirement for the diagnosis of pulmonary tuberculosis. A positive sputum may never be found in some patients with minimal lesions and in others with inactive disease.

Failure to secure positive results from sputum examination is often due to the fact that the technics applied are not sufficiently rigid. There are two important factors that determine the efficacy of sputum studies — the length of time over which the sputum specimen is collected and the method of examination. The routine smear for tubercle bacilli is notoriously unreliable. Twenty to 30 per cent of the sputums negative on direct smear are found to be positive when the sputum is examined by the concentration method. Pooled specimens, with the sputum collected over a period of three to seven days, further increases the positive findings. Multiple cultures and guinea-pig inoculation of the sputum and gastric contents should always be employed before one decides that the sputum is negative.

To avoid delay in diagnosis, the following routine is suggested. First, the use of routine smears should be avoided. These smears are so unreliable that a negative result is meaningless. Second, three consecutive seventy-two-hour pooled sputum specimens should be examined by the concentration method. If they are negative on microscopic examination, the sediment should be planted on a culture medium and inoculated into guinea pigs. Third, if the seventy-two-hour specimens are negative on microscopic examination, the next step is the immediate examination of three consecutive gastric lavages by the concentration method. Acid-fast bacilli are often found in gastric lavages when the sputum is negative, especially in children and young women. The gastric specimens should always be cultured and inoculated into a guinea pig to identify the acid-fast bacilli as tubercle bacilli.

Utilizing all available methods of examination, Pinner and Werner<sup>11</sup> have found that over 99 per cent of patients with active tuberculosis have tubercle bacilli in the sputum. Thus, when these tests are repeatedly negative in a patient with a demonstrable parenchymal infiltration in the lung that is apparently active, the lesion is probably non-tuberculous, and other diagnostic procedures are indicated.

#### DIAGNOSTIC PROCEDURES IN PATIENTS WITH SUSPECTED CANCER OF LUNG

Any patient with a visible tumor or an unexplained density or suppuration in the lung, especially if he is in the middle or older age group, should be suspected of having a pulmonary cancer. When such lesions are discovered in the minimal, asymptomatic stage, establishment of the diagnosis is most

urgent, because at this stage metastases and extension of the tumor are less likely to have occurred and surgical extirpation offers a greater chance of cure. Such patients should be bronchoscoped immediately; 60 to 70 per cent of bronchiogenic carcinomas originate in the major bronchi, and a biopsy specimen to establish the diagnosis can be obtained. All patients in whom the biopsy is positive should be explored at once, provided that no clinical evidence of metastasis or extension of the tumor is present.

If the bronchoscopy is negative, a bronchogram should be taken. At times this demonstrates an obstructing lesion in one of the smaller bronchi beyond the visual field of the bronchoscopist. A negative bronchogram, however, does not rule out a peripheral pulmonary malignant neoplasm. It is of value only when it gives positive results.

Surgical exploration of the chest is a safe procedure, and should be utilized more frequently to determine the etiology of unexplained pulmonary lesions. Physicians refer cases with unexplained abdominal disease for exploration without hesitancy, but for some unknown reason are extremely reluctant to refer patients for thoracic exploration. With modern operative technic, exploration of the chest can be performed with nearly the same degree of safety as an abdominal exploration, and with equally satisfactory results. The importance of early exploration is shown by the fact that it served to establish the diagnosis in 24 per cent of the 153 cases of carcinoma of the lung reported by Overholt.<sup>1</sup> This procedure should be used without delay in all cases with proved or suspected pulmonary or mediastinal tumors, unless evidence of metastasis or extension of the tumor is present or the age and general condition of the patient contraindicate an operative procedure.

Aspiration biopsy is used to secure tissue for pathologic study only in cases that are obviously inoperable. In patients in whom operation is possible, exploration is considered to be safer and more accurate.

#### DISCUSSION

Rienhoff<sup>12</sup> has admirably expressed the need for early diagnosis in cancer of the lung as follows: "Our clinical pace must be quickened, for until recently the great majority of recognized affections of the respiratory tract have been those in which Time was felt to be the Great Healer, but with the development of methods by which patients can not only be relieved, but cured of malignant neoplasm of the lung, it may be said that Time now takes on the role of executioner." The same idea can be applied to pulmonary tuberculosis and most of the other thoracic diseases. Almost without exception, the success of treatment is dependent on early diagnosis

and the prompt application of the indicated therapeutic measures.

Routine roentgenologic examination has been proved to be a valuable supplement, but should never be considered a substitute for a carefully taken history and a methodically performed physical examination. Occasionally, the history and physical examination point the way to the diagnosis when the roentgenogram reveals no definite abnormality. This is especially true of the early stages of bronchial disease, when the only symptom may be localized wheezing. It is also quite true of bronchiectasis, in which the presence of rales may first indicate the presence of the pathologic process.

The evidence already presented shows the value of routine roentgenologic study of the chest. This is particularly important in patients in whom the incidence of pulmonary disease, especially tuberculosis, is known to be high and the threat is known to be great, such as pregnant women and diabetic patients. The early diagnosis of pulmonary tuberculosis is important for pregnant women from the standpoint of giving proper care to the mother and adequate protection to her baby. It is important in diabetic patients because of the well-known fact that these two disease processes aggravate each other.

Another group of tuberculous patients are those in their late teens and young adults. Early diagnosis is more important here than in any other age group because of the relatively poor prognosis and the tendency for the lesions to progress rapidly. Once a lesion is discovered in a patient in this age group, it should always be considered active until proved otherwise by careful clinical and x-ray follow-up. If it is active, immediate intensive therapy and prolonged bed rest are indicated. Roentgenograms of the chest should be taken at frequent intervals, sometimes as often as once a week. In such cases, tuberculosis is not a chronic disease but one that carries a great and an immediate threat to the patient.

The responsibility for the early apprehension of pulmonary disease rests largely on the shoulders of the general practitioner and the internist, since they are the first to see the patient. Their offices should and can be the greatest case-finding agencies in the entire field of medical practice. To make this possible, the limitations of the history, the physical examination and certain laboratory procedures must be more keenly appreciated, and more rigid diagnostic procedures must be applied routinely.

## SUMMARY

Mass x-ray surveys have demonstrated that intrathoracic abnormalities, neoplasms and infections are much more frequent than has ever been suspected.

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205 Beacon Street

A series of illustrative case reports is appended.

In the light of present knowledge, some form of fully performed fluoroscopic examination.

Routine roentgenologic examination of the chest should be a routine procedure for every patient admitted to hospitals and clinics. It not only reveals more significant disease than any other routine procedure now in use, but also protects other patients and the hospital personnel from the unsuspected cases of pulmonary tuberculosis that are constantly present in hospitals.

A series of illustrative case reports is appended.

## ILLUSTRATIVE CASE REPORTS

CASE 1. J. M., a 44-year-old man, had for years had a chronic cough attributed to cigarette smoking. In March, 1942, he had blood-streaked sputum. A roentgenogram of the chest at that time showed infiltration in the right upper lobe that closely resembled a tuberculous lesion (Fig. 1A). The sputum was consistently negative. In spite of this, a

was performed. The patient made an uneventful recovery (Fig. 1D) and remained well until December, 1942, at which time he began to have low-grade fever and severe pain in the left lumbar area. He rapidly went downhill and died on February 22, 1943.

Pathologic examination of the surgical specimen revealed epidermoid carcinoma, Grade III, with metastasis to the bronchial lymph nodes. At the time of autopsy, metastases

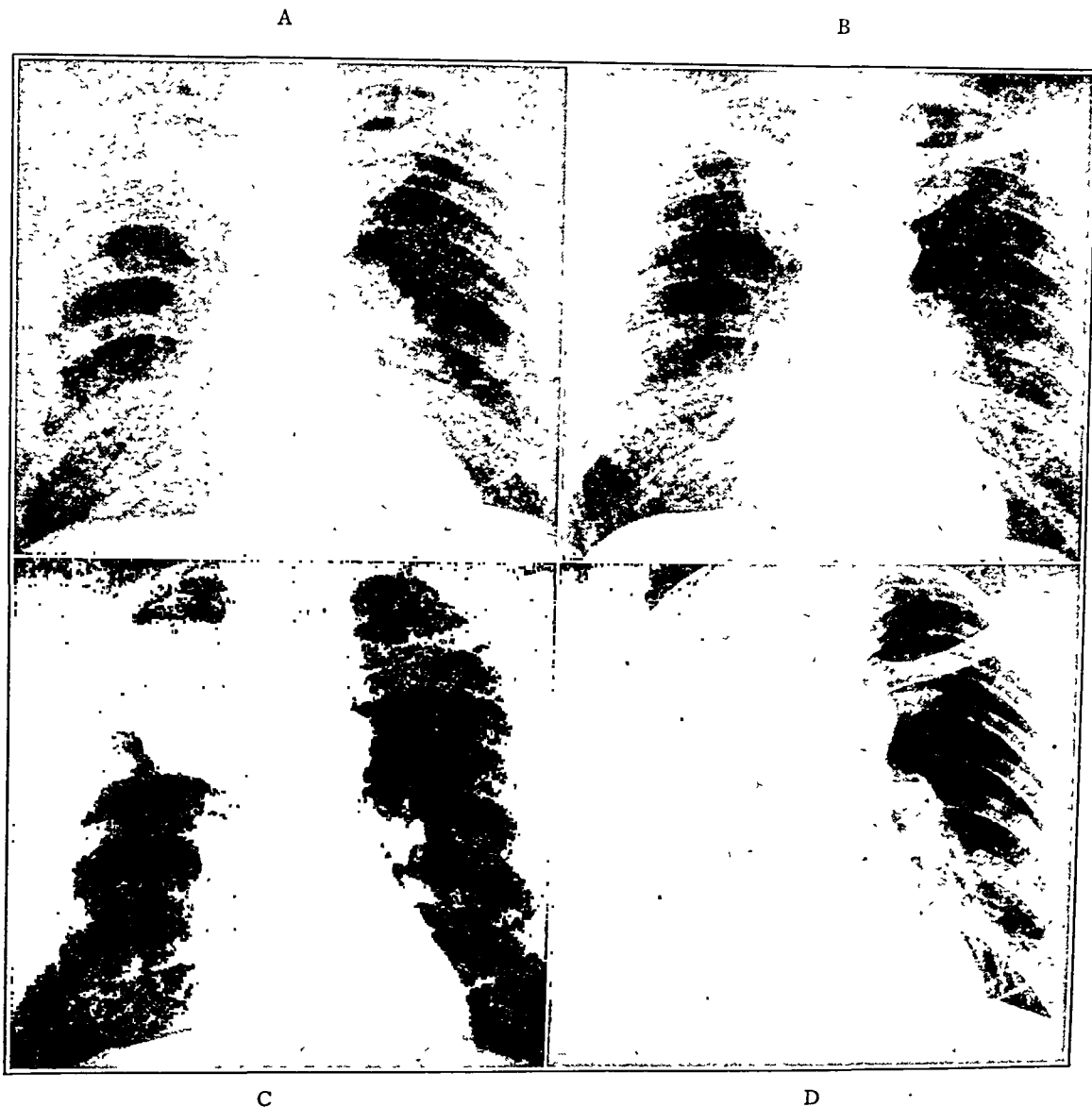


FIGURE 1. Case 1.

diagnosis of pulmonary tuberculosis was made, and the patient was sent to Florida for a few months. During that time the cough persisted but the quantity of sputum became less. There was no weight loss.

During the 4-month period following the initial roentgenogram, the shadow in the right upper lobe became quite dense and rapidly enlarged (Fig. 1B and C). A diagnosis of tumor was made and the patient was referred for surgery in August, 1942, about 5 months after the first roentgenogram of the chest. Bronchoscopy was negative. Exploratory thoracotomy was immediately performed. At operation a huge tumor mass was found in the right upper lobe. No mediastinal lymph nodes were palpable. A pneumonectomy

were found in the spleen, the left adrenal gland and the peritracheal and supraclavicular lymph nodes.

*Comment.* This case demonstrates carcinoma of the lung masquerading as pulmonary tuberculosis in its early stages. The persistently negative sputum should have indicated further diagnostic procedures. An exploratory thoracotomy at the time of the first roentgenogram would have settled the diagnosis, and pneumonectomy at that time would have offered a better chance of cure.

CASE 2. G. B., a 51-year-old man, became ill in February, 1943, at which time he was treated for "grippe." He never felt well following this, and mild cough and expectoration

continued. In July, blood streaking of the sputum first occurred. This reoccurred on several occasions. Roentgenograms revealed infiltration in the left lower lobe. There had been a weight loss of 20 pounds. The patient was treated for unresolved pneumonia. He was first seen in consultation in April 4, 1944, at which time his general condition was good and there was no evidence of further metastasis. Pathologic examination revealed a 4-by-4-cm. tumor in the lower lobe. Beyond the tumor, the lung was atelectatic and the bronchi were dilated.

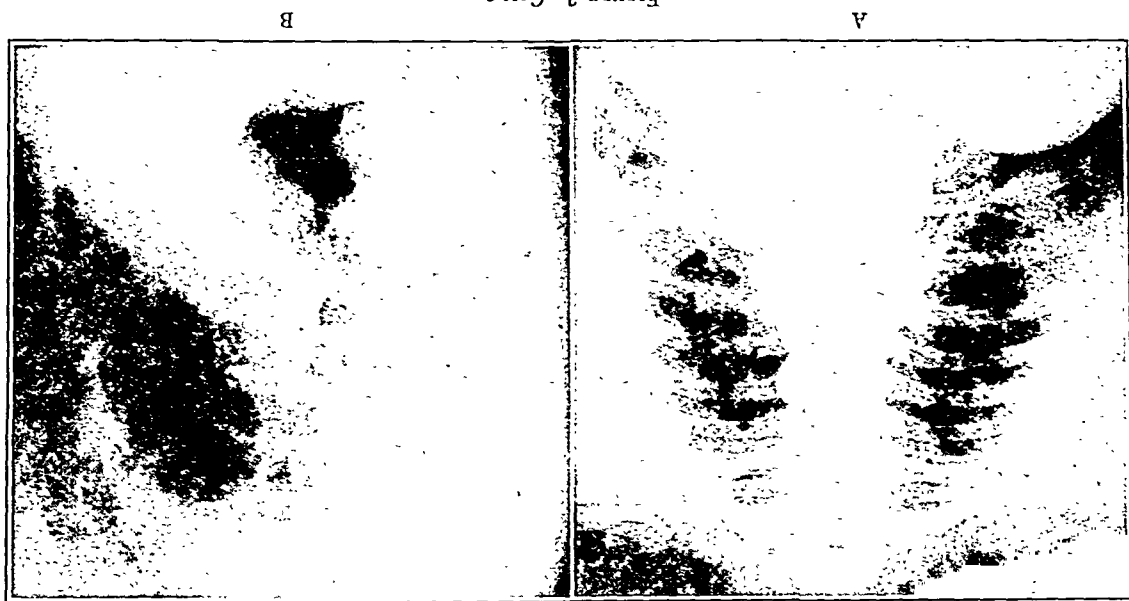


FIGURE 2. Case 2.

*Comment.* This case illustrates bronchiogenic carcinoma presenting the clinical picture of grippe at its onset. The first roentgenogram of the chest was not taken until 6 months after the onset of symptoms, and the patient was not referred for surgical treatment for another 4 months. A roentgenolobe (Fig. 2B). Bronchoscopy was negative. Exploratory lateral view showed the opacity to lie posteriorly in the lower an opacity adjacent to the left border of the heart. The roentgenogram (Fig. 2A) revealed the onset of symptoms. At that time, about 10 months after the onset of symptoms, December, 1943, about 10 months after the onset of symptoms. At that time, the roentgenogram (Fig. 2A) revealed

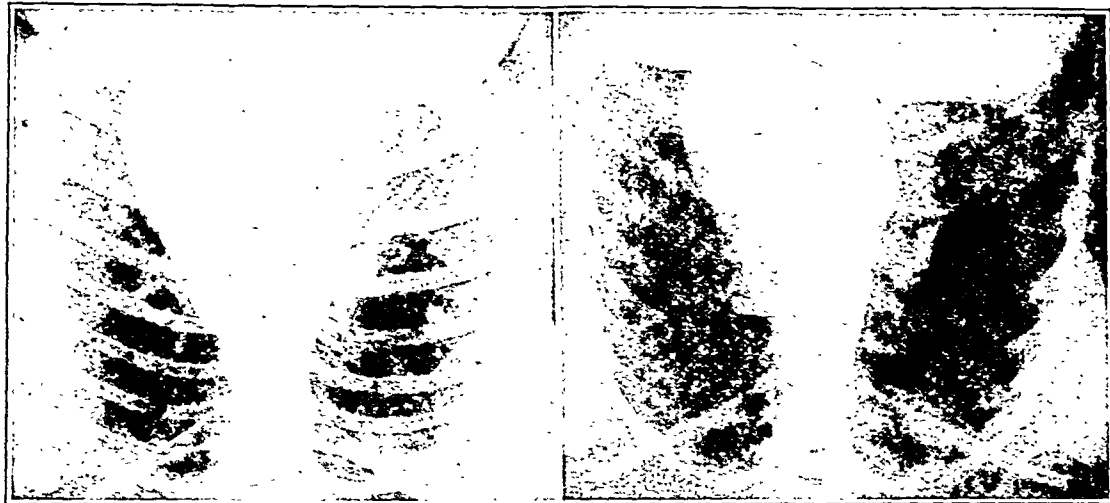


FIGURE 3. Case 3.

thoracotomy was performed and a tumor mass (epidermoid, Grade II) was found in the lower lobe, which had extended into the mediastinum around the inferior pulmonary vein. A palliative pneumonectomy was performed. X-ray therapy was used postoperatively. The patient was last seen on Case 3. D. M., a 26-year-old, married diabetic woman, had a chest roentgenogram in 1931 that revealed a small scar. A curative type of pulmonary resection might have been performed then. gram should have been taken in February, 1943, the ideal time for exploratory thoracotomy.

in the apex of the right lung. The patient was not instructed to have frequent x-ray check-ups. The next film was taken in February, 1941, and an infiltration was found in the right apex. A checkup was advised in 2 months' time. The patient failed to return, and the next roentgenogram was taken in October, 1942 (Fig 3A). At that time there was an exudative

the diagnosis and also in evaluating the course of the disease process.

CASE 4. V. S., a 51-year-old, married woman, had an acute illness in May, 1943, and was told that she had pneumonia. Following the acute episode she failed to regain her strength,

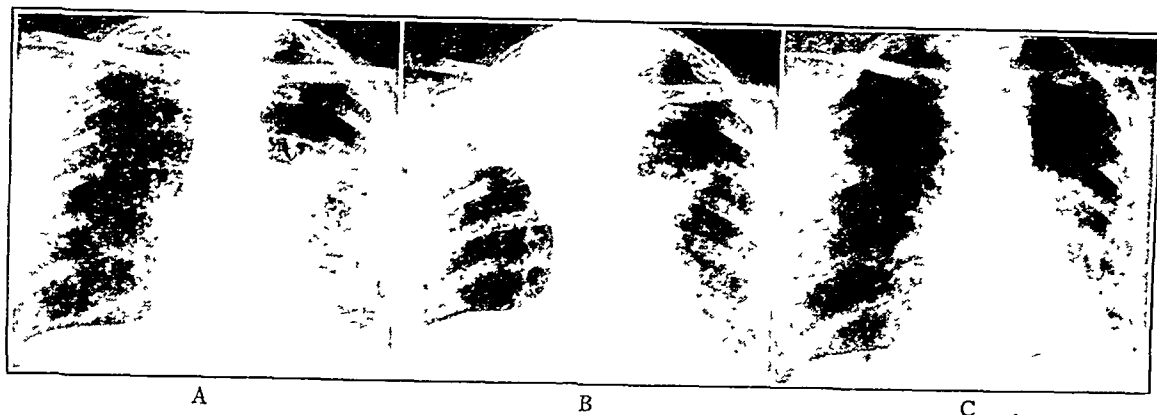


FIGURE 4. Case 4.

lesion at the right apex but no visible cavity. The patient was asymptomatic, and there were no physical signs. Crushing of the right phrenic nerve was performed, and the patient was placed on bed rest.

During the following year, x-ray films showed progressive retrogression of the lesion at the right apex, and the patient

and cough and expectoration became progressively worse. She was first seen in consultation in August, 1943, at which time the outstanding symptoms were marked cough, expectoration of 8 to 10 cc. of mucopurulent sputum daily and wheezing in the left side of the chest. A roentgenogram of the chest (Fig 4A) revealed a dense opacity in the midzone of the left lung adjacent to the hilus. The patient's age, the clinical picture and the roentgenogram all pointed to a diagnosis of bronchiogenic carcinoma. This was especially true because the sputum had been consistently negative on repeated examination by the concentration method. Bronchoscopy revealed edema and thickening of the mucosa throughout the left bronchial tree. The mucosa was also slightly inflamed and granular in appearance. No evidence of tumor was found. Bronchoscopy indicated that the process was probably due to tuberculosis. A few weeks later the sputum was proved by culture to be positive for tubercle bacilli.

The patient has been followed by bronchoscopy since then. The process extended into the trachea and eventually ulcerated. The upper portion of the right main bronchus also became involved. In October, 1943, atelectasis of the right upper lobe occurred; it disappeared within a few weeks (Fig. 4B). In recent months the patient has improved, the ulceration in the bronchus has disappeared, and the infiltration in the left lung has cleared slightly. There is now, however, a suspicious cavity in the apex of the left lower lobe (Fig. 4C).

*Comment.* This case illustrates tuberculosis masquerading as cancer of the lung. It also demonstrates the importance of rigid study of the sputum before deciding that it is negative. Bronchoscopy was helpful in establishing the diagnosis.



FIGURE 5. Case 5.

remained asymptomatic. She was x-rayed every 3 months during this time. In January, 1944, a roentgenographic check-up revealed a definite spread of the lesion (Fig. 3B). The patient still had no symptoms, and the physical examination was entirely negative.

- *Comment.* This case illustrates a silent tuberculous lesion occurring in a young diabetic patient. It demonstrates the inadequacy of the history and physical signs in establishing

CASE 5. F.R., a 55-year-old man, "caught cold" 8 weeks prior to the time he was referred for treatment. This illness subsided, and he felt well. One month later he had several hemoptyses, a low-grade fever and some malaise and had lost 15 pounds. A roentgenogram of his chest taken at the first examination on June 16, 1943, showed density in the region of left hilus (Fig. 5). Bronchoscopy was negative, and bronchograms revealed no abnormality. Exploratory thoracotomy was performed and a small tumor was found in the left upper-lobe bronchus. Pneumonectomy was performed. The patient is asymptomatic and well.

Pathologic examination of the surgical specimen showed a small Grade III epidermoid carcinoma in the left upper lobe bronchus. All the lymph nodes were normal.

*Comment.* Only 8 weeks intervened between the onset of symptoms and the time at which definitive surgical treatment was performed. This case shows the value of early explora-

tory thoracotomy in establishing the diagnosis and thus affording a good chance of cure.

Cases 6, 7, 8 and 9. These 4 patients had intrathoracic lesions that produced absolutely no symptoms. In all the diagnoses were made by routine roentgenograms of the chest.

gram of the chest taken two years previously. Figure 6C shows the roentgenogram of a 20-year-old man (Case 8) with a huge mediastinal tumor, which proved to be an adenocarcinoma; this was discovered while the patient was on active duty in the Marine Corps. Figure 6D shows the roentgenogram of a 25-year-old man (Case 9) with moderately

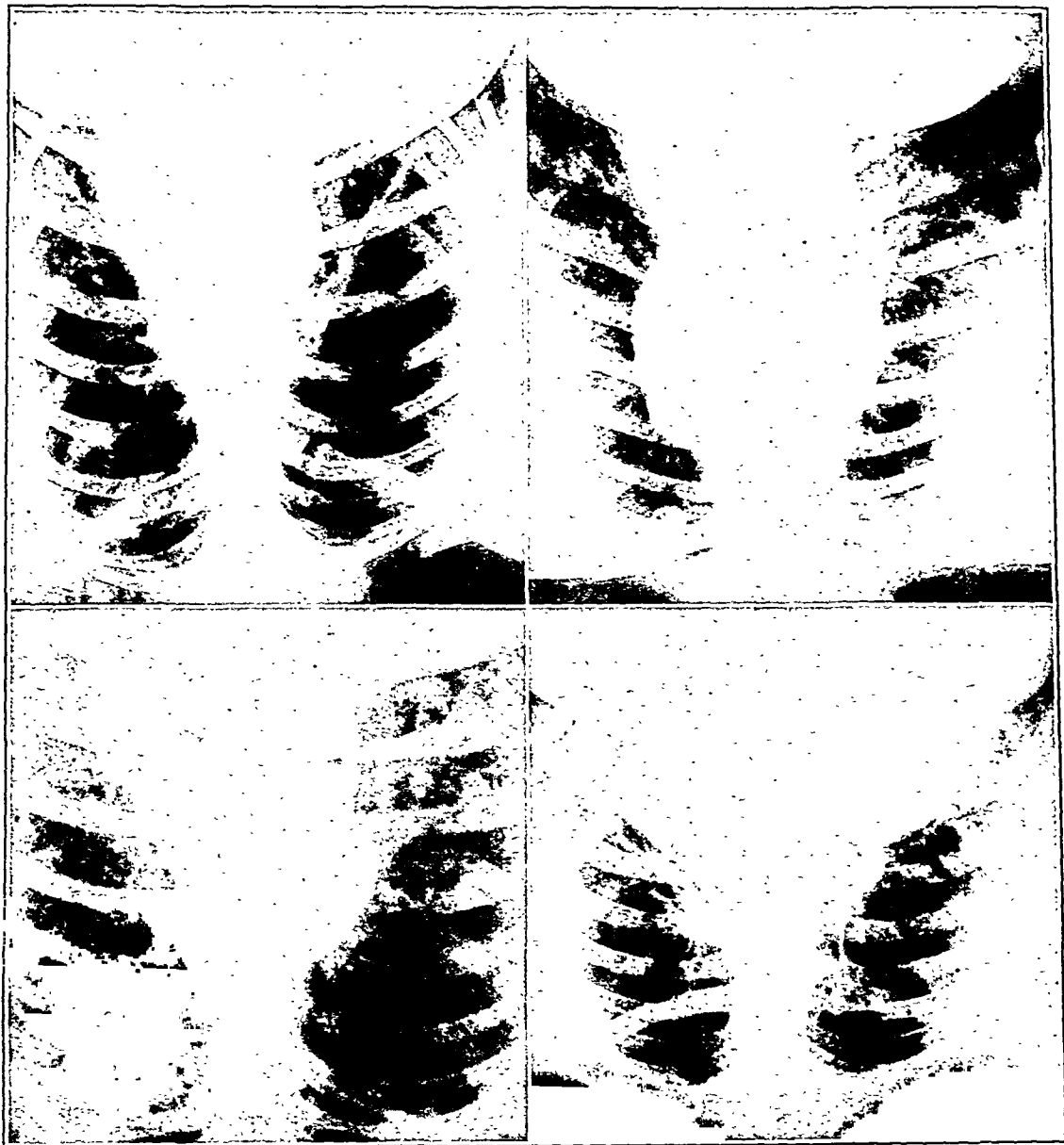


FIGURE 6. Cases 6, 7, 8 and 9.

Figure 6A shows the chest roentgenogram of a 16-year-old boy (Case 6) with a diaphragmatic hernia, which was discovered in a school survey. Figure 6B shows the chest roentgenogram of a 25-year-old student nurse (Case 7) with a mediastinal cyst into which hemorrhage had occurred; physical examination was negative, as well as a roentgenogram. Figure 6C shows the chest roentgenogram of a 20-year-old man (Case 8) with a huge mediastinal tumor, which proved to be an adenocarcinoma; this was discovered while the patient was on active duty in the Marine Corps. Figure 6D shows the roentgenogram of a 25-year-old man (Case 9) with moderately advanced pulmonary tuberculosis involving the left upper lobe; there was a 3-cm. cavity at the level of the anterior second rib, without physical signs or symptoms. The first three patients have been operated on successfully and are in perfect health; the tuberculosis of the last patient is under control with pneumothorax.

## CHALLENGES TO MEDICINE\*

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THROUGHOUT the country, many hundreds of medical students are graduating this month. Nearly all of them automatically become Army and Navy officers, scheduled to be assigned to duty in the jungles of Burma, the deserts of Africa, the snows of Alaska, the mountains of the Balkans or the interior of Germany or Japan. They, and you, can embark for duty in a far corner of the earth supremely confident in yourselves, and your complete competence to meet every situation.

If your medical education has been hastened, remember that the accelerated program has already provided new medical officers for many thousands of our fighting forces. If your classes have been crowded, know that there will be fewer doctors for the civilian population after the war than before the war, despite acceleration and increased enrollments. If your teachers have been reduced in numbers, be sure your medical education is still far superior to that obtainable anywhere in the world, even in peacetime. If you have been beset from day to day with numberless uncertainties, recall that you share doubts with the entire civilized world.

We have supreme confidence in you, in your ability to discharge your obligations not only in this great conflict, but in the equally difficult readjustments to be made after the war.

Medical students, medical faculties, medical scientists — all of American medicine — may well hold their heads high in any accounting that is held of contributions to winning the war. Thousands of men who would have died in the last war will return to useful and happy lives because of plasma, penicillin, surgery, air evacuation of the wounded and because of the medical officers — because of you. We know that as you have met your responsibilities in the past you will carry on the proud tradition of service in the immediate future during this conflict, and we know that you will likewise accept with resolution the challenges of the future in the world of peace, which will even transcend in importance the tasks of today. The problems to be met are those of education, adjustment to civilian life and expansion of the effectiveness of medicine in a changing world.

## EDUCATION

The last war was won by food. "Food will win the war." It was won by the United States, with her fresh, strong forces. The war was won by the

French holding fast before Paris, by the British blockade of Germany, by the defection of the German people, by the German sailors at Kronstadt, by the American skilled worker — by everyone who participated.

This war will see fewer such credit lines. Perhaps we have become mature. German is still taught in our colleges, and many medical schools still require it for admission. Wagner still fires the pulse, and we continue to trust Goethe, who could say to a world less sick than ours, "Thou ailest here, and here, and here."

We have reached maturity, perhaps, and we shall not say, "Brains won the war, education won the war." Education has done its stint. Colleges, universities and professional schools have made available their entire educational resources, and many many thousands of men will be better citizens in peacetime for the education they received for war.

I need not recount to you the many Army Specialized Training and Navy programs. You are familiar with the numerous projects in operation: radar and radiography; parachute physiology and parasite detection; planes and plasma.

Education for war has been universal, but the education of soldiers for peace has also taken place. The Armed Forces Institute offers correspondence courses in any subject and at every level, to every soldier or sailor with leisure for study. An educational project under the Army Education Branch is planning to serve the demands and intellectual curiosities of thousands of soldiers in the interim between the surrender of Germany and that of Japan. It is anticipated that many thousands of men will spend weeks to months in Europe before the crowded transport facilities of that time will be able to carry away the last of our armies to America or the Pacific. How can that time be most profitably utilized? For many, it will be a period of formal organized education. Scores of courses are now being developed in all the fields of learning, from the level of the high school to advanced university work. Textbooks have been selected and outlines prepared for courses varying from one to several months. Wherever possible, physical educational facilities in Europe will be used, including the modest school buildings of the small cities and the laboratories of the great universities. The instructors will come from the officers and men. Here a private who has had a year of college will give instruction in high school biology; there a Ph.D. will give college instruction.

Some of the educational projects and programs of this war approach the fantastic. Vice-Admiral Ross

\*Convocation address, delivered at Boston University School of Medicine, Boston, September 22, 1944.

†Secretary, Council on Medical Education and Hospitals, American Medical Association; professorial lecturer in physiology, University of Chicago.



We already know something of the magnitude of the problem. It is now nearly two years since the Council on Medical Education and Hospitals of the American Medical Association anticipated the problem to be faced, and set about to meet it, collaborating with hospitals, American boards in the specialties, medical schools and, most recently, the Committee on Postwar Medical Services. This committee was established by the American Medical Association, in collaboration with the American College of Physicians and the American College of Surgeons. Representation is also included from the Association of American Medical Colleges, the American Hospital Association, the Federation of State Licensing Boards of the United States, the Catholic Hospital Association, the Procurement and Assignment Service, the Advisory Board for Medical Specialties and the Veterans Administration. A major project of this committee has been a study of the postwar educational desires of medical officers, which is being conducted in co-operation with the surgeons general of the Army, Navy and Public Health Service. Questionnaires on the postwar educational desires of medical officers have been sent to all physicians in all branches of the Service. Returns are now being received at the American Medical Association headquarters in great numbers. Transferred to punch cards, this information will be systematically analyzed and given wide publicity, so that each state medical society, each medical school and each hospital will be made aware of its responsibilities.

Analyses of the first 1000 returns have been published by Lieutenant Colonel Harold C. Lueckh<sup>2</sup> and the Council on Medical Education and Hospitals.<sup>3</sup> The report of the Council indicates that considerable expansion is required in providing facilities in all fields, and for periods ranging from several weeks in refresher and review courses to many months in internships and residencies. Of the 1000 officers, about 20 per cent indicated that they planned no further postwar training. Eighty per cent—mainly younger officers—desired some additional education. About one third of those who replied desired six months or less of training, and nearly half desired hospital training of six months or more.

To meet the requirements of returning medical officers for additional training is a serious responsibility that will require the continued joint efforts of the Committee on Postwar Medical Service, the Council on Medical Education and Hospitals, the Health Service, hospitals approved for internships and residencies, the American boards in the medical specialties, medical schools, state licensing boards, the Veterans Administration, foundations, county and state medical societies and every institution capable of providing advanced training to physicians.

McIntire, Surgeon General of the Navy, tells of clinics held in midocean. In a convoy not in trouble, or in a task force on a long journey, the medical officers in the many vessels of the fleet meet at a stated time on one of the larger vessels. Here are assembled, under the direction of competent medical officers of higher rank, selected cases of general interest and stubborn diagnostic problems encountered in any large body of men subject to illness or injury. A clinic is held, especially for the instruction of the younger officers whose hospital training has been curtailed. This is medical education that may be characterized as unconventional, at least.

At the University of Edinburgh, in Scotland, an event unique in medical annals is occurring. When Poland was overrun, thousands of Polish officers and men and civilians were evacuated to England. Many of these had been medical students. Among the medical officers were a goodly number of teachers from the Polish medical schools. The University of Edinburgh provided classroom, laboratory and clinic facilities, and there was set up the first medical school in the history of any country in which citizens of the country taught their fellowmen in their own tongue in a foreign land. The Polish Medical School of Edinburgh has graduated two classes of future Polish doctors, and has made a respectable contribution in research. This amazing experiment in international medicine will yield incalculable dividends in the rebirth of medicine and education in Poland, which the Germans boast has now been reduced to an intellectual desert.

In the midst of our efforts here at home to produce competent medical officers at the maximum rate, consistent with high quality, we are deeply concerned with your future continuation training. Despite the wartime educational efforts mentioned, we may be sure that when the balance is struck, the debits will far outweigh the credits, in all fields of education. In medicine, this will be reflected in a lower quality of medical care after the war, unless the challenge is met resolutely and wisely.

Recent graduates are keenly aware of their deficiencies. They have been compelled to complete their training under unfavorable conditions. Teaching staffs have been depleted while their teaching loads have been increased and the tempo of education hastened. The internship has been necessarily reduced to an inadequate nine months, a period barely sufficient to make the discerning student aware of the medical problems he will face in the practice of medicine but utterly insufficient to do more than start him on the way to their solution. Medical educators are likewise keenly aware of the necessity for providing, after the war, continuation courses and advanced hospital training not only for new generations of medical graduates but for the returning medical officers as well.

## CHALLENGES TO MEDICINE\*

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THROUGHOUT the country, many hundreds of medical students are graduating this month. Nearly all of them automatically become Army and Navy officers, scheduled to be assigned to duty in the jungles of Burma, the deserts of Africa, the snows of Alaska, the mountains of the Balkans or the interior of Germany or Japan. They, and you, can embark for duty in a far corner of the earth supremely confident in yourselves, and your complete competence to meet every situation.

If your medical education has been hastened, remember that the accelerated program has already provided new medical officers for many thousands of our fighting forces. If your classes have been crowded, know that there will be fewer doctors for the civilian population after the war than before the war, despite acceleration and increased enrollments. If your teachers have been reduced in numbers, be sure your medical education is still far superior to that obtainable anywhere in the world, even in peacetime. If you have been beset from day to day with numberless uncertainties, recall that you share doubts with the entire civilized world.

We have supreme confidence in you, in your ability to discharge your obligations not only in this great conflict, but in the equally difficult readjustments to be made after the war.

Medical students, medical faculties, medical scientists — all of American medicine — may well hold their heads high in any accounting that is held of contributions to winning the war. Thousands of men who would have died in the last war will return to useful and happy lives because of plasma, penicillin, surgery, air evacuation of the wounded and because of the medical officers — because of you. We know that as you have met your responsibilities in the past you will carry on the proud tradition of service in the immediate future during this conflict, and we know that you will likewise accept with resolution the challenges of the future in the world of peace, which will even transcend in importance the tasks of today. The problems to be met are those of education, adjustment to civilian life and expansion of the effectiveness of medicine in a changing world.

## EDUCATION

The last war was won by food. "Food will win the war." It was won by the United States, with her fresh, strong forces. The war was won by the

French holding fast before Paris, by the British blockade of Germany, by the defection of the German people, by the German sailors at Kronstadt, by the American skilled worker — by everyone who participated.

This war will see fewer such credit lines. Perhaps we have become mature. German is still taught in our colleges, and many medical schools still require it for admission. Wagner still fires the pulse, and we continue to trust Goethe, who could say to a world less sick than ours, "Thou ailest here, and here, and here."

We have reached maturity, perhaps, and we shall not say, "Brains won the war, education won the war." Education has done its stint. Colleges, universities and professional schools have made available their entire educational resources, and many many thousands of men will be better citizens in peacetime for the education they received for war.

I need not recount to you the many Army Specialized Training and Navy programs. You are familiar with the numerous projects in operation: radar and radiography; parachute physiology and parasite detection; planes and plasma.

Education for war has been universal, but the education of soldiers for peace has also taken place. The Armed Forces Institute offers correspondence courses in any subject and at every level, to every soldier or sailor with leisure for study. An educational project under the Army Education Branch is planning to serve the demands and intellectual curiosities of thousands of soldiers in the interim between the surrender of Germany and that of Japan. It is anticipated that many thousands of men will spend weeks to months in Europe before the crowded transport facilities of that time will be able to carry away the last of our armies to America or the Pacific. How can that time be most profitably utilized? For many, it will be a period of formal organized education. Scores of courses are now being developed in all the fields of learning, from the level of the high school to advanced university work. Textbooks have been selected and outlines prepared for courses varying from one to several months. Wherever possible, physical educational facilities in Europe will be used, including the modest school buildings of the small cities and the laboratories of the great universities. The instructors will come from the officers and men. Here a private who has had a year of college will give instruction in high school biology; there a Ph.D. will give college instruction.

Some of the educational projects and programs of this war approach the fantastic. Vice-Admiral Ross

\*Convocation address, delivered at Boston University School of Medicine, Boston, September 22, 1944.

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McIntire, Surgeon General of the Navy, tells of clinics held in midocean. In a convoy not in trouble, or in a task force on a long journey, the medical officers in the many vessels of the fleet meet at a stated time on one of the larger vessels. Here are assembled, under the direction of competent medical officers of higher rank, selected cases of general interest and stubborn diagnostic problems encountered in any large body of men subject to illness or injury. A clinic is held, especially for the instruction of the younger officers whose hospital training has been curtailed. This is medical education that may be characterized as unconventional, at least.

At the University of Edinburgh, in Scotland, an event unique in medical annals is occurring. When Poland was overrun, thousands of Polish officers and men and civilians were evacuated to England. Many of these had been medical students. Among the medical officers were a goodly number of teachers from the Polish medical schools. The University of Edinburgh provided classroom, laboratory and clinic facilities, and there was set up the first medical school in the history of any country in which citizens of the country taught their fellowmen in their own tongue in a foreign land. The Polish Medical School of Edinburgh has graduated two classes of future Polish doctors, and has made a respectable contribution in research. This amazing experiment in international medicine will yield incalculable dividends in the rebirth of medicine and education in Poland, which the Germans boast has now been reduced to an intellectual desert.

In the midst of our efforts here at home to produce competent medical officers at the maximum rate, consistent with high quality, we are deeply concerned with your future continuation training. Despite the wartime educational efforts mentioned, we may be sure that when the balance is struck, the debits will far outweigh the credits, in all fields of education. In medicine, this will be reflected in a lower quality of medical care after the war, unless the challenge is met resolutely and wisely.

Recent graduates are keenly aware of their deficiencies. They have been compelled to complete their training under unfavorable conditions. Teaching staffs have been depleted while their teaching loads have been increased and the tempo of education hastened. The internship has been necessarily reduced to an inadequate nine months, a period barely sufficient to make the discerning student aware of the medical problems he will face in the practice of medicine but utterly insufficient to do more than start him on the way to their solution. Medical educators are likewise keenly aware of the necessity for providing, after the war, continuation courses and advanced hospital training not only for new generations of medical graduates but for the returning medical officers as well.

We already know something of the magnitude of the problem. It is now nearly two years since the Council on Medical Education and Hospitals of the American Medical Association anticipated the problem to be faced, and set about to meet it, collaborating with hospitals, American boards in the specialties, medical schools and, most recently, the Committee on Postwar Medical Services. This committee was established by the American Medical Association, in collaboration with the American College of Physicians and the American College of Surgeons. Representation is also included from the Association of American Medical Colleges, the American Hospital Association, the Federation of State Licensing Boards of the United States, the Catholic Hospital Association, the Procurement and Assignment Service, the Advisory Board for Medical Specialties and the Veterans Administration. A major project of this committee has been a study of the postwar educational desires of medical officers, which is being conducted in co-operation with the surgeons general of the Army, Navy and Public Health Service. Questionnaires on the postwar educational desires of medical officers have been sent to all physicians in all branches of the Service. Returns are now being received at the American Medical Association headquarters in great numbers. Transferred to punch cards, this information will be systematically analyzed and given wide publicity, so that each state medical society, each medical school and each hospital will be made aware of its responsibilities.

Analyses of the first 1000 returns have been published by Lieutenant Colonel Harold C. Luehrs, and the Council on Medical Education and Hospitals.<sup>3</sup> The report of the Council indicates that considerable expansion is required in providing facilities in all fields, and for periods ranging from several weeks in refresher and review courses to many months in internships and residencies. Of the 1000 officers, about 20 per cent indicated that they planned no further postwar training. Eighty per cent—mainly younger officers—desired some additional education. About one third of those who replied desired six months or less of training, and nearly half desired hospital training of six months or more.

To meet the requirements of returning medical officers for additional training is a serious responsibility that will require the continued joint efforts of the Committee on Postwar Medical Service, the Council on Medical Education and Hospitals, the surgeons general of the Army, Navy and Public Health Service, hospitals approved for internships and residencies, the American boards in the medical specialties, medical schools, state licensing boards, the Veterans Administration, foundations, county and state medical societies and every institution capable of providing advanced training to physicians.

On the basis of the estimated demands for educational opportunities, the Council on Medical Education and Hospitals of the American Medical Association is already engaged in a ten-point program aimed at filling these needs. Internships, residencies, fellowships, graduate externships, and review and refresher courses are being developed to meet these needs. This is a solemn obligation we owe to the young physician now at war, who has given so much, so freely and so well. But there is also the added obligation to ensure that a high quality of medical care will be maintained in this country, lest the health of the Nation should suffer for years to come. You who graduate today may count on us who lay these plans to do our utmost for your continuation training after the war.

#### ADJUSTMENT TO CIVILIAN LIFE

Those of you who remember Remarque's great novel of the last war, *All Quiet on the Western Front* will recall with deeper feeling his novel of the peace that followed, *The Road Back*. War still poisoned the returned German soldier, even in the green meadows and wooded hills of his childhood. Here he did not relive the games of school picnics but, crouching behind a tree, noted at once what a perfect defense could be made there. He saw on that hill an artillery battery, and in that grove two machine-gun nests. There were snipers in the shrubbery. There was a perfect trap, with withering crossfire.

We escaped the Hun hatred of the last war that included an unreasonable hatred of German literature and music. Perhaps we shall be sufficiently civilized also to avoid the psychologic perils of the coming peace. Perhaps Remarque's character will be supplanted with the young infantryman I recently met on a train from the South. He was en route to Fort Sheridan to be discharged. The "fruit salad" on his left chest included three combat stars. I said: "Well, the war is over for you. And now what will you do?" He chuckled his response: "I'm going back to the farm. I'll rest awhile, maybe two weeks, with breakfast in bed every morning. Then I'll go to work. We have a fine farm. We raise corn and hogs."

Every returning soldier will face his own peculiar problem in his adjustment from a life of hardship where every decision was made for him to a life less hard but requiring him to do the deciding. Medical officers will face their own special problems.

When the war ends, thousands of physicians will have known no other form of medical practice than that of completely socialized medicine. The group practice of medicine is not socialized medicine. Neither is salaried medical practice, or hospital or sickness insurance. Socialized medicine is a system in which all doctors are paid from tax moneys, no patient pays his doctor directly, and all patients are provided with free medical care. This form of

practice is necessarily the rule in the armed forces. Army and Navy medicine is completely socialized, and is the form of practice of one third of the active physicians of the United States today.

In the armed forces, everyone who needs medical care must get it. The economic status of the patient is never even considered. The only criterion for the best of treatment is the need of the patient. Every resource of medical science must be employed when available and indicated: plasma or penicillin, surgery or psychiatry, regardless of cost. No obstacle can be too great to surmount, whether it may require eight natives to carry a single wounded soldier to a medical station in the Owen Stanley Mountains, or a fleet of air transports to carry the injured from the fields of France to a hospital in England.

There is no doubt that wartime experiences of physicians and of patients will stimulate increased efforts toward the provision of improved medical care for everyone, but without that necessary total regimentation that must obtain in the armed forces. Such regimentation is complete, in every phase of the life of both the doctor and the patient. The patient is ordered to appear before the doctor, and the doctor in turn may order the patient to the hospital. This has not been possible in civilian life. It is very disturbing to everyone who is interested in providing the best medical care for everyone to examine certain hospital statistics in this country. If the various states are arranged in the order of number of available hospital beds per 1000 people, it is seen that the same order is followed in the percentages of those beds that are occupied. But the correlation is the reverse of what we should expect. In general, those states having the fewest hospital beds have the lowest rates of occupancy of those beds. States with most beds use them most.

Why this is true we do not know. It may be that in those states that lack the money for hospital beds the people lack the money to use them. It may be that some of these hospitals do not provide a high grade of medical care. It may also be that the people do not sufficiently demand medical care even when it is available, because of ignorance, superstition, prejudice or sheer inertia. Even among the more fortunate classes of people, full use is not made of available medical facilities. I dare say that virtually everyone here would subscribe to the principle of an annual physical examination for everyone. Yet extremely few seek such examinations, even in normal times, unless compelled by an insurance, employment or other requirement, or unless frank illness sets in.

The demand for medical care in civilian life is different from the need for it. One of our major goals must be educational: to inform people of the facilities available and the necessity for using them. Such a program of education of the public for the prevention of disease should center about the hos-

The educational responsibilities of the hospital become twofold: the training of medical graduates and the informing of the public. These considerations, these consequences of war and the practice of medicine in the armed forces, carry us to the third of the major challenges that must be met by the medicine of tomorrow.

#### EXPANDING THE EFFECTIVENESS OF MEDICINE

The drives that have carried American medicine to its present high position will continue, and will carry it far beyond the present frontiers of service to mankind. The first of these undeniable urges is the spirit of scientific inquiry. It made Von Alering and Alinkowski wonder why their operated dogs voided urine containing sugar, and it kept Banting and Best from quitting when their first experiments on diabetic dogs were inconclusive. It gave the world insulin.

This urge impelled Whipple to try empirically all the edibles that occurred to him in the treatment of dogs he had made anemic, and it stimulated Alnot and Murphy to extend the observations to human beings. And today, we have the liver treatment of pernicious anemia. But though we can now control these formerly fatal disorders, we still do not know their basic cause. We cannot prevent them, and when treatment is suspended, the diabetic or the pernicious anemia patient is as seriously ill as ever. The first causes are still unknown and uncontrollable. The successes of the past provide ample hope, however, that this challenge will also be met, not only in diabetes and pernicious anemia but in hypertension, infantile paralysis and cancer, as well as in meeting the problems of a more equitable distribution of medical care.

Scientific experimentation not only must provide the solution of the problems of control of disease but also must guide us in determining the forms that medical practice shall take in the future. Medical science plans experiments, measures results and plans further experiments, to the end of greater and greater understanding of man in health and disease. This same spirit must direct us in solving the equally complex problems of man's relation to his fellows and the place of medicine in a changing social and economic structure.

Changes will come. You will be involved in them. In part, you will direct them. In so far as you exert influence, you should be impelled by the impartial spirit of inquiry that served you so well in your pursuit of the truth in the medical sciences. We must recognize the extreme complexity of the problem. To state that doctors are attracted to cities because they can make more money there is a gross oversimplification. Cities provide the essential tools for the practice of medicine, which have been many times multiplied — x-ray equip-

ment, electrocardiographs, other laboratory facilities, consultation services and, above all, hospitals. The economic level in many rural communities, and in many counties in the United States, makes it impossible for those communities, unaided, to provide either doctors or the necessary facilities for doctors to carry on their work. It seems clear that hospital facilities will be lacking or will remain at a substandard level in many rural communities in the United States unless there is increased state and federal aid for hospital construction and equipment, the organization of clinics and the development of traveling clinics, to be operated under local control.

But even if all this were provided for the country physician, problems of distribution of medical care would remain. The doctor demands, in common with his civilized fellows, a life with stimulating social, intellectual and cultural contacts. Good schools, homes, churches, music and comradeship may loom as large in his selection of a community to practice in as income, x-ray facilities or hospitals. The distribution of medical care is only one aspect of the larger problem of elevating the general economic level of large numbers of our population in peacetime. If unemployment is kept as low as now, and production is maintained at the present level after the war and dedicated to the welfare of the people, the problems of distribution of medical care will be greatly diminished.

Difficult though these problems are, they must be attacked. Here, as in science, experimentation provides the most promising approach. New experiments are being planned almost daily, and the reports are rapidly accumulating. The California Physicians Service, under the auspices of the San Francisco County Medical Society, is rapidly increasing the scope of its services. About a year ago, the rate of growth of the Service was about 1000 new members a month. Today, 6000 members a month are being added, although the net gains are less than these figures indicate because of the turnover in employment.

The Prepaid Medical Service in Connecticut is operating on a cash-indemnity basis under the auspices of the Connecticut State Medical Society. The Committee on Medical Economics of the Kansas Medical Society is developing a prepayment plan for certain medical services. In Michigan it is reported that one person in nine is covered by Michigan Medical Service certificates, and one in five by those of Michigan Hospital Service.<sup>1</sup>

The Missouri State Medical Association has unanimously adopted a plan of prepayment for medical and surgical care in hospitals, to be known as Missouri Medical Service, Inc. In Nebraska, the Nebraska State Medical Society has adopted a resolution providing for the study of insurance plans and organization of such a plan for Nebraska.

Numerous other plans have been in operation, for varying periods, on a statewide or county basis, under the auspices of the medical profession. This is true in Colorado, Massachusetts, New Jersey, New York, Pennsylvania, Utah, Texas, Kansas, Delaware and North Carolina. These plans must be looked on as experiments in the more complete and equitable distribution of medical care.

As in the fields of the more exact sciences, these experiments in medical sociology are likely to turn out to be poorly conceived, in some instances, and often the results may be difficult to interpret. But the all-important fact remains: experiments in the distribution of medical care are in progress, and we may hope that they will be as fruitful as those that provided insulin for diabetes, liver for pernicious anemia and penicillin for infections.

We are impelled to continue experiments of this kind, as well as experiments in carrying patients to the doctors with adequate modern facilities, recalling the air transport of the wounded in battle, instead of struggling to provide doctors and hospitals for every community. We must experiment with traveling clinics and the closer integration of diagnostic, hospital and expert consultation services. Above all, we must experiment rather than design blueprints in the skies; we must follow the methods of science, not the promptings of the emotions.

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You who are graduating are heirs to a glorious heritage of the past. And you face a challenge unequaled in the past. We will afford every help in

the furtherance of your educational aims. We will assist you in your adjustment to civilian practice. And we enlist your enthusiastic endeavors to make the art and science of medicine, which you have so well learned, available to all who need it.

We know that you will serve your fellows selflessly. Despite your trials, you, and all of us who have remained at home, have little justification for complaint. All of us here owe so much to our friends and allies. A recent medical graduate in Britain<sup>5</sup> has put it well:

It is hard for my immediate generation to forget that their services have been paid for already, by the bodies of men no stronger and brains no less trained. It is difficult to say that we deserved it, even when it was part of a well-laid, state-planned calculation. We were reserved, held out of the line, while Jock (who was trained as a diplomat) took his platoon behind the enemy lines to destroy thirty-six aeroplanes and was killed by a bleeding artery on the way home; and Michael died when he led his company on to the last objective at El Alamein (he had passed his final examination before ordination); and Melvin bombed the dam when he could have stayed comfortably in the RAF in America. If such people had not given up their jobs and gone to war we should not be doctors now. It is my salutary misfortune to remember how much they entertained the world without trying, and helped the world without the special equipment of medicine.

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## MEDICAL PROGRESS

## INSECT VECTORS OF DISEASE

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tion is being exposed to the potential hazards of disease throughout the fighting zones and in those areas to which the troops are moved. This risk of infection will probably not reach its peak during the actual warfare, but rather in the period of population readjustment following the cessation of hostilities.

Large numbers of nonimmune susceptible persons are being concentrated in areas where insect-borne diseases are prevalent. With battles raging in all parts of the globe and principally in the tropics and subtropics,<sup>9</sup> new hazards face the fighting men. Under battle conditions, they are being exposed to the added risk of the limitation of known effective control measures, unavoidable in the face of combat. To the classic list of military diseases, such as dysentery, typhoid, paratyphoid and typhus fevers and malaria,<sup>10</sup> the military personnel have now the added risk of an entire galaxy of tropical diseases,<sup>11</sup> many of which are insect borne. The problem presented by latent unrecognized infection<sup>12</sup> and the carrier state among the military personnel cannot be fully appreciated. The similar problem presented by refugees in mass emigration from war-devastated areas or because of postwar treaties cannot be fully anticipated. The danger to the civilian population of the United States does not arise from the recognized and treated cases but from those with latent infections, from carriers and from refugees, all of whom may bring infections back to their homes and thereby infect the indigenous arthropod vector.<sup>13-15</sup>

In the present war, arthropod-borne diseases have already played an important role.<sup>16</sup> Typhus fever has reached epidemic proportions throughout eastern Europe and has extended into all of Europe, North Africa and Asia Minor.<sup>17, 18</sup> The hazards of insect-borne diseases have been intensified by the crowding in bomb shelters and concentration camps. Scabies, impetigo and lice infestations are acute problems. The incidences of typhus fever<sup>19</sup> and of relapsing fever, which had been decreasing during the decade preceding the war, have again increased in Poland, Russia and Rumania, which are the principal European foci of these diseases. Similarly, malaria has again taken its toll, but to a far greater degree.

Alan has, to a large degree, been able to control those infections for which he has been able to develop an artificial immunity by inoculation, such as smallpox and typhoid fever, and those diseases against which isolation is an important factor. Under wartime conditions, however, the control of infectious diseases is of military importance only

Under war conditions, many of the safeguards of the health of both the military and civilian populations are abandoned.<sup>2</sup> The crowding of people, the primitive environmental conditions and the lack of personal hygiene are all conducive to the spread of infectious disease. The concentration and movement of large groups of population — civilian and military — and the limitless hardships, with fatigue, general malnutrition,<sup>3</sup> famine and exposure, and the lack of medical care experienced by civilians and some armies, provide the fuses for the explosion of epidemics.

More soldiers have invariably been killed by infectious disease than by bullets in all wars prior to the Franco-Russian War of 1870, when the German Army reported an excess of deaths from battle.<sup>4</sup> In the Russo-Japanese War of 1904, both sides maintained the high proportion of deaths from wounds. In spite of the toll of influenza, the American Expeditionary Forces of 1917-1918 reported fewer deaths from sickness than from battle; although for the entire United States Army, at home and abroad, the deaths from disease were more numerous. During and after World War I the usual war diseases were highly prevalent in eastern Europe.<sup>5</sup> There was an epidemic of typhus fever throughout Russia, Poland and Serbia. Fortunately, the disease did not spread to western Europe. Malaria was victor in Macedonia and decimated the opposing armies to a tragic ineffective fraction.<sup>6</sup>

Although it had previously disappeared from most of Europe,<sup>7</sup> malaria returned with the soldiers and evacuees to central, eastern and northern Europe to ravage the population. The United States Army, fortunately, escaped any extensive involvement of insect-borne disease, as the zone of military operations did not extend into areas where these diseases were endemic.

This global war is much more hazardous to civilian health than any in history.<sup>8</sup> The civilian population

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in so far as these interfere with the task assigned to any military unit<sup>20</sup>; and therefore, the main purpose of infectious disease control during wartime is guided by the principle of keeping as many men physically fit and in fighting trim as possible. In other words, the importance of a disease from a military point of view and the value of disease-control measures are determined in wartime by their effect or noneffect on the available fighting strength of a force.<sup>21</sup> Insect-borne diseases are perhaps the most difficult and among the most important diseases with which military personnel are afflicted. For example,<sup>22</sup> malaria was one of the main forces that defeated the American troops at Bataan<sup>23</sup>; it again assumed major importance in the Solomons and on Guadalcanal.<sup>24</sup>

A disease is classified as insect-borne<sup>25</sup> when a blood-sucking insect is the sole or the usual agent by which the infecting organisms are transmitted from one patient to another. This transmission may be from man through vector to man, from animal through vector to man, from animal through vector to animal and from man through vector to animal. The disease may have a wide host selectivity, and the vector may spread the disease from one genus of animals to another. On the other hand, many insects feed only on certain closely related species of the same animal, whereas other vectors are not so finicky about the type of blood they suck. Many insects prefer certain hosts and fly many miles to obtain this favorite blood, rather than bite some other species that may be near by. Occasionally, this zoophilic deviation of the insect vector can be used as a control measure in malaria.<sup>6</sup> The importation of cattle may deviate the mosquitoes from man and thereby reduce the incidence of bites of man.

An insect-borne disease may be transmitted by only one genus or, in some instances, by only certain species or merely one species of insect. Other insect-borne diseases are spread by several different insects, entirely unrelated and of different genera. Dengue,<sup>26</sup> for example, was thought to be transmitted naturally by only two species of *Aedes* mosquitoes, *Aedes aegypti*<sup>27</sup> and *A. albopictus*,<sup>28</sup> but *A. scutellaris hebrideus* has been recently incriminated.<sup>29</sup> Malaria is transmitted by some twenty species of Anopheline mosquitoes.<sup>30</sup> Relapsing fevers are transmitted by both lice and ticks; and typhus fever by lice,<sup>31</sup> fleas<sup>32</sup> and mites.<sup>33</sup>

#### CLASSIFICATION OF VECTORS

Many so-called "insect-borne" diseases are not transmitted by insects but by other genera.<sup>34, 35</sup> The true insect is a hexapod and belongs to the class Insecta, such as the mosquito, fly, bedbug and louse. Other diseases are transmitted by the class Arachnida, which are eight-legged creatures, such as mites and ticks. The phylum including both the insects and the arachnids is Arthropoda — animals with jointed legs.

The class Insecta is composed of about twenty orders, of which five are incriminated directly or indirectly in the transmission of disease. These orders are Diptera (flies and mosquitoes), Anoplura (lice), Siphonaptera (fleas), Hemiptera (bugs) and Orthoptera (roaches). To these may be added sixth order, Hymenoptera (wasps, bees and ants) some of which bite or sting man and are a source of discomfort. Perhaps some future research may relate these insects to disease transmission.

The class Arachnida is composed of eleven orders of which only one, Acarina, comprised of ticks and mites, is known to transmit disease. The order Scorpionida (scorpions) and Araneida (spiders) cause discomfort by biting man but have not been incriminated as vectors of disease.

Arthropods may affect the health and well-being of man in several ways: by conveying disease, by invading the tissues of man, as in scabies, by inoculating poisonous substances,<sup>36, 37</sup> such as in the bite of the black-widow spider, bee or wasp, and by being pests to man, such as bedbugs. This paper, however, is limited to a brief discussion of the diseases conveyed by arthropods and those of the arthropods themselves.

#### DIPTERA

##### *Mosquitoes*

The most important arthropods responsible for the transmission of disease are the true insects, in particular mosquitoes and flies. Mosquitoes transmit filariasis,<sup>38</sup> malaria,<sup>7</sup> leishmaniasis,<sup>39</sup> tularemia,<sup>40</sup> yellow fever,<sup>41</sup> dengue fever,<sup>26</sup> Rift Valley fever, equine encephalomyelitis,<sup>42</sup> Japanese encephalitis<sup>43</sup> and St. Louis encephalitis.<sup>44</sup> Not all mosquitoes are vectors of disease; moreover, only the female is dangerous, as the proboscis of the male is not sufficiently rigid to penetrate the skin and hence it aesthetically lives on plant juices. Three mosquito genera are of special importance as vectors — Anopheles (malaria), Aedes (dengue fever, filariasis and yellow fever<sup>41</sup>) and Culex (filariasis, equine encephalomyelitis, Japanese encephalitis and St. Louis encephalitis).

Not all species of any genus are capable of transmitting disease, nor are all such species of equal significance as vectors. The important vector in any particular geographic area may be missing or unimportant in some other location. For example, in the United States by far the most important vector of malaria is *Anopheles quadrimaculatus*<sup>45</sup>; in Italy, *A. maculipennis labbranchiae*; and in Brazil, *A. gambiae*.<sup>46</sup> Although all mosquitoes develop by complete metamorphosis and the life cycle consists of eggs, larva, pupa and adult, all species do not breed under similar conditions.<sup>47</sup> Some species have only one brood a year, whereas others continue to breed throughout the year. Some lay their eggs in water-filled tree holes, and others prefer collections of water in tin cans and cisterns; still others breed in ponds, marshes, hoof-prints, puddles,



warm sunny ponds, cool running streams, or even brackish water.

The eggs of *Anopheles* are deposited singly in batches of forty to one hundred on the surface of the water and are provided with floats.<sup>48</sup> *Aedes* eggs are also laid singly in lots of twenty-five to fifty; they sink to the bottom, or when laid on the side of water receptacles, they may lie dormant for months, hatching only on favorable conditions of temperature and moisture.<sup>49</sup> *Culex* eggs are deposited on the water surface in rats of one hundred to four hundred.<sup>50</sup> In twelve to seventy-two hours the eggs hatch into larvae, which are actively mobile and feeding cylindrical organisms; they vary in color from gray, yellow or red brown to dark brown or black. Developing by repeated moulting, the larvae pass through four instars or forms, increasing each time in size. Under favorable conditions, the larval stage lasts about ten days. *Mosquito* larvae must breathe through a tube at the posterior end of the body. All mosquito larvae except those of *Anopheles* have a distinct siphon tube, by which they attach themselves to the surface of the water, the head being suspended downward. Since all species of *Anopheles* have only a tubeless opening, they lie parallel with the surface of the water, their heads being just under the surface. This position makes them more susceptible to poisoning from small particles that may float on the surface of the water. From the fourth instar, the larva develops into a comma-shaped pupa, which is a resting, floating stage during which a complete metamorphosis from larva to adult transpires. The nonfeeding pupae are supplied with two breathing trumpets on the dorsum; they are actively motile, being supplied with two paddle-shaped appendages. Locomotion is accomplished by rapid flexion and extension of the abdomen.

In about twenty-four to seventy-two hours the pupal case splits along the dorsum and the adult or imago gradually emerges, and as soon as the exoskeleton hardens the mosquito is ready for flight and food. Temperature and humidity affect the biting activities, mosquitoes usually being more active in hot humid weather. The flight range varies with different species; the flight of *Anopheles quadrimaculatus* is usually less than a mile, whereas *Aedes sollicitans*, a salt-water species, has been found fourteen miles from the nearest salt water.<sup>51</sup> Moreover, mosquitoes, as well as other arthropods, may be transported by motor vehicles, ships and airplanes. Sailing vessels were responsible for transporting *Aedes aegypti* to Boston and other American ports from South America,<sup>52</sup> thereby causing short-lived local outbreaks of yellow fever. The aeroplane was probably responsible for the importation of *Anopheles gambiae* to Brazil from Africa, thereby causing an extensive and severe outbreak of malaria.<sup>53</sup> The adult female mosquito, under favorable conditions, usually lives as long as three months. Fortunately, however, many succumb to the vicissitudes of their environment — natural enemies, adverse weather and other unfavorable conditions. Hence, the normal life expectancy of a female adult mosquito is probably two to four weeks.<sup>54</sup> Certain species of mosquitoes, however, hibernate throughout winter as adults. Thus, *Culex* and *Anopheles*, in temperate zones, survive as gravid females and some species of *Anopheles* hibernate as larvae. *Aedes* usually survives from one breeding period to another as eggs. In colder regions nearly all species survive winter as eggs, but in the tropics and subtropics unfavorable periods may be survived by retarded or slowed development.

The biting, breeding and flight habits of mosquitoes vary from place to place and from one species to another. It is therefore absolutely necessary to conduct a mosquito survey or to have available detailed information relative to the particular insect-borne disease, its vectors and the ecological factors that are likely to bear an important role in the determination of effective and efficiently employed control measures.<sup>55</sup> These factors may also influence the location of camps or semipermanent institutions, such as airfields and hospitals, in relation to other population groups or settlements in the general vicinity. Similarly, the success of a military campaign may be adversely affected by lack of true evaluation of the vectors and their habits. The identification of mosquitoes is a difficult but necessary task.<sup>56</sup> It is usually accomplished by a key prepared for certain geographic sectors.<sup>55, 56</sup> Such identification into species is performed with a dissection microscope and may usually be done on both larvae and adults. *Mosquito* control measures must be guided by preliminary identification surveys,<sup>57</sup> as well as by periodic catches of both larvae and adults to evaluate the effectiveness of applied measures. Control measures must be selective and applied only to those species that are vectors of the disease for which control is being exercised, since money, time and labor might otherwise be expended lavishly for controlling harmless mosquitoes. Similarly, nuisance mosquitoes must be controlled if effective results are to be expected. *Mosquito*-control measures are usually classified as temporary or permanent.<sup>58</sup> Temporary measures are the application of larvicides,<sup>59</sup> spraying with insecticides<sup>60</sup> and the use of insect repellents.<sup>61</sup> Permanent control measures include flooding,<sup>62</sup> drainage and the construction of ditches, dams or special siphon apparatus<sup>63</sup> for the automatic changing of water levels. The choice of method<sup>64</sup> depends on the availability of time, labor and funds and the desired result.

### Flies

Whereas all true mosquitoes belong to the family Culicidae, suborder Nematocera of the order Diptera, flies are members of three suborders.<sup>65</sup> The suborder Nematocera includes moth flies, midges and gnats, all of which contain members that are

disease vectors and are blood-sucking insects. The suborder Brachycera includes the large-bodied horseflies and deer flies. One genus, *Chrysops*, blood-sucking flies, includes the vector of tularemia and of loasis, a filarial disease. The remainder are important to man only as pests, many not being blood suckers. The suborder Athericera includes the common housefly and related "filth" flies. They are important in the mechanical transmission of disease, especially under primitive environmental sanitation and on the battlefield; many of their larvae are myiasis producing. Some are vicious biters and pests of man. One genus, *Glossina*, contains the vector of African sleeping sickness.

Identification of flies depends on classification into suborders on their antennal characteristics and thereafter on the structure of their mouth parts, wings and body. Any dipterous insect possessing mouth parts capable of piercing the skin of man must be regarded as a potential vector of blood-inhabiting, pathogenic micro-organisms; insects with nonpiercing mouth parts obviously cannot be responsible for introducing infection directly into the circulation except through previously injured surfaces. Thus, by inspection of the mouth parts, the insect's disease-conveying hazard may be estimated.

*Nematocera.* Of the suborder Nematocera, family Psychodidae, only one genus, *Phlebotomus*, is blood sucking and responsible for transmitting disease.<sup>66</sup> Pappataci fever (sandfly fever),<sup>67, 68</sup> bartonellosis (oroya fever)<sup>69</sup> and leishmaniasis (kala azar and oriental sore<sup>70</sup>) are transmitted by *Phlebotomus*. In addition to being vectors the sandflies are vicious biters.<sup>71</sup> *Phlebotomus* flies are minute in size and have extremely hairy bodies and wings. As in mosquitoes, only the female is capable of biting and spreading disease. Eggs of these flies are deposited in batches of fifty in dark, moist crevices in walls, caves and embankments. The larvae feed on organic and excremental debris. After four months a naked pupa is formed, from which the adult emerges; the life cycle is six to eight weeks from egg to adult.

The adults of the nonbiting species of Psychodidae are frequently found in kitchens and out-houses, along creeks filled with decaying matter and about sewage-disposal plants. The larvae are found in decaying vegetable matter, sewage, manure, exuding sap of trees and foul streams.

The *Phlebotomus* sandflies lay their eggs in crevices of rocks and in damp cracks in shady soil or floors.<sup>72</sup> The adult sandfly varies from 1 to 3 mm. in length and hence can crawl through the meshes of an ordinary mosquito net. Its bite is extremely annoying and may cause a great deal of irritation. The females feed exclusively on blood; they often feed once and die after oviposition, but most species feed at least twice or oftener. They are nocturnal and seldom bite except at night; in some places they

seem to forage for only an hour or two after sunset. During the day they hide in darkened corners, cellars and crevices and under floors and rocks. Their flight is limited, and when disturbed on walls, they usually fly only a few inches. Their breeding places are nearly always within a few hundred feet of where they feed. Dimethyl phthalate has been used as a repellent in control of *Phlebotomus*.<sup>71</sup>

The same suborder contains the family Simuliidae, which has only one disease-transmitting genus, *Simulium*, the buffalo gnats and black flies. Species of *Simulium* act as vectors of larvae of *Onchocerca volvulus*, the filaria responsible for onchocerciasis.<sup>73</sup> Female buffalo gnats are also vicious and persistent biters. The eggs, in masses of five hundred, are small, glistening and yellow; they are laid on stones and vegetation in swiftly running streams. The larvae, by a posterior sucker, attach themselves to rocks and maintain their position in the current. The brown or green larvae move from one spot to another and tend to congregate in dense, slimy, mosslike groups on stones and other substrates. The full-grown larvae become enclosed in cone-shaped cocoons below the surface of the water. The entire life cycle requires ten to thirteen weeks, but *Simulium* may hibernate through the winter either in the egg or in the larval stage. Since black flies breed in running water, the methods to be employed in their extermination are quite different from those ordinarily used. The reducing of river flow by damming at intervals, leaving falls between, or, in the case of small brooks, the construction of underground channels are effective measures. In some instances, sweeping stones and other substrates with brooms is of value. Furthermore, the clearing of debris from a stream deprives the larvae of a fastening place. Repellents that are effective against mosquitoes also afford protection against black flies. These flies rarely enter houses, hence fumigation is usually unnecessary. Smudges are beneficial for the protection of both men and animals. The black fly bites freely during daylight.

A third family, Ceratopogonidae, of the same suborder, Nematocera, contains sandflies, no-see-ums, biting midges and punkies. This family includes three genera, of which one, *Culicoides*,<sup>74</sup> is the vector of filaria. Although species of *Acanthocheilonema* and *Mansonella* are considered nonpathogenic to man, they are extremely annoying to both man and animals wherever they are abundant. These flies are extremely small and have light and dark ornamental markings on the wings. Only the female bites. Eggs are usually laid in water or water-saturated sand or soil. The white threadlike larvae develop into slender brown pupae, which may be mistaken for mosquito pupa because of two short breathing tubes on the thorax. The life cycle requires six to twelve months; *Culicoides* go through the winter either in the egg or in the larval stage.

The great majority of the species that attack man

They are mechanical transmitters of disease and household pests to man.

The genus *Glossina*, which includes all species of tsetse flies,<sup>78</sup> is chiefly limited to tropical Africa; these flies are the vectors of Gambian and Rhodesian sleeping sickness. Both the male and female are blood sucking. The female is viviparous and carries a single larva at a time. This larva is deposited, fully developed, in dry sandy soil in shady places. The larva burrows down about 5 cm. and pupates. One species occurs in the southwestern corner of Arabia. Tsetse flies<sup>79</sup> are by no means evenly distributed over these great areas, being limited locally to the so-called "fly-belts," chiefly along rivers and at the edges of lakes. They are migratory, especially from minor water collections that may be drying up to larger and more permanent bodies of water. They are diurnal in habits. *Glossina palpalis* is most active in the middle of bright days, and *G. tachinoides* on dull days and in the morning. *G. morsitans* is active in the morning and afternoon but disappears at midday; *G. brevipalpis* and *G. longipennis* bite from sunrise until about 8:00 a.m. and from about 4:00 p.m. until dark. Tsetse flies are attracted by color, especially black and brown, and are repelled by white. When accompanied by flies. Black or dark clothes are preferred to light-colored ones, and khaki appears particularly attractive to them. Insect repellents, flyproof clothing or veils and the wearing of white clothing are effective control measures. Passing through the fly-belts at night is the best method of avoiding tsetse flies. Clearing away brush along streams infested with *G. palpalis* and *G. tachinoides* is effective in preventing breeding. Tsetse flies seldom go more than fifty yards from the brushy borders of streams except when following prey, when they may fly several hundred yards. Therefore, if brush is cleared away for thirty yards from the edges of water in the vicinity of fords, villages, washing places and so forth, the flies quickly disappear.

Stomoxys, the stable fly, has been frequently used in the experimental transmission of disease. Although naturally infected specimens have not been found, it is best to consider it as a potential vector of tularemia and other diseases. It is about the size of the common housefly, often enters houses, especially before rains, and is responsible for the belief that the housefly bites. *Stomoxys calcitrans* may be noted resting in sunny places on the walls of stables and farm buildings.<sup>80</sup> It breeds primarily in excrement and often can be recovered in abundance in scattered material at the edges of old hay- and strawstacks and in the organic debris often washed up along the seashore. The flies are cosmopolitan in distribution, and control measures are principally local procedures to eliminate breeding in such material.

and animals belong to the genus *Culicoides*, which lays its eggs on or near water, the larvae living in water or in water-saturated mud or sand. Many favor brackish or salt water. A few species belong to other genera, *Leptocnops* and *Forcipomyia*, which breed for the most part in damp places under bark, stones and moss. Nearly all the blood-sucking species become active at dusk; if disturbed, they also bite on bright days in the shade. They are active flies, often going over half a mile in search of food, but only when the air is still. The bites of *Culicoides* produce nettle-like pricks, which may be followed by burning sensations and intolerable itching. Control by larvicides is impractical; smoke smudges and oily repellents seem to be more effective. Because of their small size they can penetrate ordinary screen and nets.

*Brachycera*. The suborder *Brachycera* contains only one family, *Tabanidae*, with only one genus, *Chrysops*, that transmits human disease. Horse-flies, deer flies and mango flies are common names for flies of this suborder. Females of the species of the genus *Chrysops* are vectors of tularemia<sup>81</sup> and loasis.<sup>82</sup> Two other genera, *Tabanus* and *Hematomia*, are important only as pests. Some species act as pests to animals and transmit certain animal diseases, such as anthrax, surra, el dehab and swamp fever; they have also been incriminated in Russia as vectors of tularemia.<sup>83</sup> Eggs, in gelatinous masses, are laid on leaves of aquatic plants overhanging sloughs and swamps. In about a week, the larvae hatch and drop into the water or moist ground. They are elongated, tapering sharply at both ends, and have marked ridges at each segment. In several months the fully developed larvae work their way into drier ground, pupate and in two or three weeks emerge as adults. The life cycle requires three to twelve months; overwintering occurs in the egg or larval stage.

Because of their peculiar breeding habits, horse-flies, deer flies, mango flies, green-headed flies and other *Tabanidae* are difficult, if not altogether impossible, to control in the immature stages. Oil films on water may be effective in killing larvae as they hatch from eggs and drop into the underlying water. *Aihircera*. This suborder, family *Alusidae*, contains one genus, *Glossina*, that is a vector of a human disease, African sleeping sickness. Other genera of *Alusidae* are important as mechanical carriers of typhoid and paratyphoid fevers, cholera and bacillary and amebic dysentery. In a large number of genera, the larvae may be tissue parasites of man, producing myiasis. The blood-sucking group of these flies include the genera *Glossina*,<sup>84</sup> *Stomoxys* and *Haematobia*; they are vicious biters and vectors of disease. The nonblood-sucking flies include the genera *Alusca*, *Fannia*, *Hippelates*, *Sarcophaga*, *Calliphora*, *Chrysomya* and *Lucilia*.

Species of *Haematobia*, horn flies, are a serious pest of cattle but rarely attack man. They are blood-suckers and closely resemble the housefly.

*Musca domestica*, the common housefly, develops in animal and vegetable refuse that accumulates about farms and houses.<sup>81</sup> It is almost ubiquitous since its preferred larval foods are manure and fecal wastes, which are usually available near human habitation. It is responsible for the mechanical transfer of enteric disease-producing micro-organisms from fecal material to food.<sup>82-84</sup> It is often mistaken for the stable fly, *Stomoxys calcitrans*, and the latrine fly, *Fannia scalaris*. The latter is frequently seen hovering in mid-air in the middle of the room.

The housefly develops by complete metamorphosis, through the egg, larval, pupal and adult stages each of which requires certain definite environmental conditions.<sup>85</sup> The white, glistening oval eggs are about 1 mm. in length and are deposited in masses of one hundred to one hundred and fifty on or in moist organic matter. The female lays two to four batches in her lifetime. At 85 to 90°F., the eggs hatch in eight hours; at temperatures of 60 to 68°F., in twenty-four hours; and below 40°F., in two or three days. The cylindrical, gray or creamy-white, segmented, wormlike larvae or maggots are highly mobile and burrow into the fermenting mass, reaching maturity in four or five days under favorable conditions. The larvae leave the moist warm environment and migrate to pupate in a dryer and cooler place. The immobile, brown pupal stage lasts three to ten days, whereupon the adult fly emerges, crawls upward through the soil or manure and, as soon as the wings harden, is ready to fly. The female reaches sexual maturity and oviposition begins in from two and a half to twenty days. Under proper environmental conditions the egg-to-adult metamorphosis may be as short as seven days. The optimal temperature for flies is about 90°F.; they are quickly killed in wet material at 108°F. or by a temperature of 115°F. in a dry environment. The housefly does not bite. It cannot ingest particles larger than 0.045 mm. in diameter. Larger substances, such as grains of sugar, are first dissolved by regurgitation of liquid. The housefly is attracted to food principally by odor; it is a persistent and greedy feeder, storing food in its crop, an esophageal diverticulum. The normal flight range of the housefly does not exceed one thousand yards; however, if food is lacking they may migrate as far as a mile, principally in the direction of the prevailing winds. The usual life span is about one month. In the fall many flies are killed by a parasitic fungus disease, *Empusa muscae*. Houseflies are rendered inactive by low temperatures and are killed at 10 to 15°F. They hibernate over winter in the larval or pupal stage.

Green-bottle flies belong to the genera *Lucilia* and *Chrysomya*. They are scavenger flies, de-

positing their eggs on fish and decaying meat, on human and animal excrement and in open wounds. The thorax and abdomen of *Lucilia* are metallic green or bluish green and lustrous. The life cycle is similar to that of the housefly. The gray "flesh" flies, *Sarcophaga*, have a large body. The female is larviparous. The bluebottle flies, *Calliphora*, are scavengers, feeding on fish, decaying meat and human or animal excrement. They are of robust size and have a blue or metallic sheen to their bodies. All these flies may act as mechanical vectors of enteric infections.

The eye gnats, *Hippelates*, are vectors of yaws and of infectious conjunctivitis.<sup>86</sup> They are small in size and persistently return to feed on lachrymal secretions even though repeatedly brushed away. They do not bite but have spines on their mouth parts that cause lesions of the skin, through which infection may take place.

Certain species of flies can produce myiasis, a condition wherein fly maggots or larvae live parasitically in the organs and tissues of man and animals. Clinically, myiasis may be classified according to the part of the body invaded.<sup>87</sup> The larvae of *Chrysomya bezziana* are the usual cause of human myiasis in India. Other examples are species of *Dermatobia*,<sup>88</sup> tropical warble flies, and of *Hypoderma*, cattle botflies. Other flies that normally live in decomposing matter but which occasionally lay eggs in living tissues, being attracted by foul discharges and blood, are *Chrysomya macellaria*,<sup>89</sup> the American screw worm, and species of *Lucilia*, green-bottle flies and of *Sarcophaga*, gray flesh flies.

The eggs or larvae of some flies may be swallowed, usually in food or drink. The larvae often develop in the intestine,<sup>90</sup> but this occurrence is accidental and not a part of the normal development. Examples of this type of myiasis-producing flies are included in the genera *Calliphora*, *Sarcophaga*, *Musca*, *Fannia*, *Eristalis* and *Stomoxys*.

(To be continued)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31111

#### PRÉSENTATION OF CASE

A forty-three-year-old factory proprietor was admitted to the hospital because of increasing dyspnea and dependent edema.

The patient was well until three years prior to admission, when he developed shortness of breath on exertion, edema of the ankles and legs, and weakness. He was admitted to a community hospital, where he was treated for heart failure over a period of four weeks, following which he returned to work believing himself to be entirely well. He continued to work and, except for an increasingly bloated feeling, was essentially free from symptoms until about one year prior to entry, when he again developed dyspnea and edema, progressing to a point that made hospitalization necessary. He remained in the hospital for twelve weeks and was discharged improved, but some dyspnea and edema were still present. He was unable to return to work, remaining at home resting and receiving diuretic injections once or twice a week. In spite of these measures, he noted a gradually increasing bloated feeling and abdominal distention. He was admitted to the hospital for study.

The patient recalled no childhood illness or definite rheumatic infection. He had had an attack of gonorrhea thirteen years previously and had recovered promptly after treatment. He had lost about 20 pounds in one and a half years.

Physical examination revealed a rather thin man in no acute distress who became somewhat short of breath on slight exertion. The skin appeared moderately atrophic over the whole body, and there was little subcutaneous tissue. Pitting edema was present, most marked over the sacrum, extending up the back, and to some extent in the lower extremities. There was questionable early clubbing of the fingers. The pupils reacted slowly to light and accommodation. There was some stiffness and limitation of motion of the neck in all directions, with poor muscles and a large, dilated, pulsating vein on the right. There was moderate scoliosis, with the thoracic concavity to the right, and slight lordosis. The thoracic cage showed little motion and flared out asymmetrically. There was dullness

at both bases, more marked on the left, with decreased fremitus and diminished breath sounds. No rales were heard. The heart appeared enlarged. The left border of dullness was about 9.5 cm. from the midsternal line and 1 cm. outside the mid-clavicular line. There was questionable enlargement to the right. The point of maximum impulse could not be felt. The rhythm was irregular, with an extra beat and an occasional coupling for short periods. The sounds were of fair quality. A Grade 2 to 3 systolic murmur was audible over the lower end of the sternum and apex. No diastolic murmurs were heard. The liver extended to the level of the umbilicus. It was firm and nontender, with a smooth surface and a smooth sharp edge. The spleen was easily palpable, firm and nontender. The radial arteries were thickened but not tortuous, and no pulsations could be felt in the pedal vessels. There was some limitation of motion in all joints, especially the elbows, but there was no pain or crepitus on manipulation.

The temperature was 98.6°F., the pulse 50, and the respirations 16. The blood pressure was 110 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 4,610,000, with 13.6 gm. of hemoglobin, and a white-cell count of 10,200, with 78 per cent neutrophils, 8 per cent lymphocytes, 10 per cent monocytes, 2 per cent eosinophils and 2 per cent basophils. The red cells and platelets were normal. The urine had a specific gravity of 1.016, with a + test for albumin and a few white cells in the sediment. The serum protein was 4.4 gm. per 100 cc. A blood culture was negative. A blood Hinton reaction was negative. A bromsulfalein test showed 15 per cent dye retention in the serum. An antecubital-vein-to-mouth circulation time with Decholin was 36 seconds. The venous pressure ranged between 12 and 15 cm., the veins filling and emptying with the heart cycle.

A roentgenogram of the chest revealed considerable fluid in the left pleural cavity obscuring the diaphragm and producing some compression of the lower lobe. A small amount of fluid was also present in the right costophrenic sinus. The visible lung fields were clear except for a healed Ghon's complex on the right, with calcification in both hili. The heart showed a marked general enlargement, with a transverse diameter of 17 cm., as compared to an internal chest diameter of 27.5 cm. Pulsations of the heart were slow, but the amplitude was within normal limits. There was no dilatation of the left auricle. Examination of the esophagus showed no delay in the passage of barium and no evidence of varices.

An electrocardiogram on admission (Fig. 1) revealed an almost regular ventricular rhythm, with a rate of 60, and frequent ventricular premature beats from varying foci. There was no discernible auricular activity. There was an extremely low

\*On leave of absence.

at the time of onset was forty-three years old — not twenty-three, or sixty-three, but forty-three. In the second place, he had been having symptoms for something in the neighborhood of three years; for over a year these had been more or less fixed but present most of the time. It seemed to me as I read the story that over a three-year period he had had rather less fluctuation in the course of his disability than many people with progressive types of cardiac disease. I began to think about the kinds of cardiac disease, if this should turn out to be cardiac disease, which can give a slowly progressive, fixed type of

voltage of the QRS complexes, and almost flat T waves in the standard leads, with slight sagging of ST<sub>1</sub> and ST<sub>2</sub>. Lead  $\pm$  showed an absent R, a slightly elevated ST and a flat T.

The patient was placed on a cardiac regimen, including a low-salt diet, limitation of fluids, 0.1 gm. of digitalis daily, ammonium chloride and Mercupurin. An electrocardiogram on the seventh hospital day showed no change except for disappearance of the ventricular premature beats and a somewhat slower rate. Precordial leads revealed a tendency to low voltage, with absent R waves in Leads 1, 2,



FIGURE 1. Electrocardiogram on admission.

disability. There are several conditions that will do that.

One immediately thinks of tricuspid stenosis.

With tricuspid stenosis there is apt to be a long history of peripheral congestion, with enlargement of the liver, often with edema but without the fluctuations that are frequent in people who are suffering from variations in the capacity of the myocardium. There are many reasons to believe that this man did not have tricuspid stenosis. In the first place, he did not have mitral stenosis, and to have tricuspid stenosis without its older brother is extremely unusual. He had no signs of it in his murmurs, and no suggestion in his x-ray films, nor did he have the degree of venous distention that is usually compatible with that as a primary situation.

If he did not have tricuspid stenosis, had he some other variety of obstruction? It is striking that he had no evidence of acute congestion of the lungs,

3 and 4. The T waves were low and upright in Leads 1 and 2, diphasic in Lead 3 and inverted in Leads 4, 5 and 6.

The patient continued unchanged except for a brief upper respiratory infection on the tenth and eleventh hospital days, during which the temperature rose to 102°F. but rapidly returned to normal.

The pulse continued slow. A left thoracentesis on the twenty-third hospital day was productive of 150 to 200 cc of clear straw-colored fluid, which was negative on culture.

On the twenty-fourth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

Dr. C. SIDNEY BURWELL\*: I should like to draw the picture of the way this disease began. In the first place, it seems to me significant that the patient

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that he had primarily peripheral congestion and that the dyspnea was never paroxysmal and was not present at rest but occurred when he tried to exert himself. This suggests that the dyspnea was due to inability on his part to increase cardiac output or the respiratory volume.

Another type of obstruction to circulation that he might have had is pericardial disease. If he had pericardial disease with this history it would certainly have been chronic pericardial disease, and it might have been that interesting disorder called "constrictive pericarditis," which Dr. White<sup>1,2</sup> began to study actively in 1928. I shall come back to that presently.

A third possibility is pulmonary heart disease with cor pulmonale. This would account for slow progression without much fluctuation. Cor pulmonale is an interesting disorder, which may be based on a good many kinds of changes in the pulmonary circulation and which is usually marked by right ventricular failure. Perhaps he had right ventricular failure, but he had no cyanosis, no evidence of extensive lung disease, no history of cough anywhere in this record. If he had cor pulmonale he must have had an unusual form of primary pulmonary hypertension, and I do not find any evidence of it. There are other disorders that lead to right-sided failure, and the most frequent is mitral stenosis. He might have had mitral stenosis, with right ventricular failure of a rather fixed type, but the evidence in the murmurs, in the history and in the x-ray films is against it.

Could this form of symptoms result from a myocardial infarct on the basis of vascular disease? Occasionally, although rarely, one sees vascular degeneration of the myocardium almost limited to the right ventricle. In such a situation this history might be possible.

I want to consider in a moment the possibility that this was not cardiac disease at all, at least not primarily, because there are certain interesting suggestions that other organs were involved in an important way. Before doing that, I should like to review and perhaps get a little help on one or two bits of evidence that are presented. In the first place, the venous pressure is recorded as equivalent to 12 to 15 cm. of water. It is particularly necessary in a man with an abnormal chest to know how that was measured. How was the zero point determined?

DR. EDWIN O. WHEELER: It was determined by measuring 5 cm. down from the sternum rather than 10 cm. up from the back.

DR. BURWELL: I should also like to know what the anteroposterior diameter of this man's chest was.

DR. WHEELER: I do not know.

DR. BURWELL: Could you guess? Was it increased or normal?

DR. PAUL D. WHITE: I should say that it was normal.

DR. BURWELL: That is comforting. On this x-ray film it looks increased. Would you agree, Dr. Holmes?

DR. GEORGE W. HOLMES: Yes.

DR. BURWELL: These measurements are important. Assuming that this is a cross section of the chest and the heart is lying here, if you measure 5 cm. down from the sternum, you hit the level of the right auricle. If you measure 10 cm. up from the back, you hit about the same level. If a man has an emphysematous chest, that relation of the heart to the back does not change, but the anterior chest wall in effect is lifted off the heart. Thus, if you measure 5 cm. back from the sternum, you set your level above the right auricle and therefore get a false low venous pressure. Every now and then one sees obvious right ventricular failure and a normal venous pressure, and in a fair percentage of these patients the normality of the venous pressure is the result of error in the placing of the zero point. When you put it somewhere near the position of the right auricle you find that the pressure has a high pressure. I take it that this man had venous distention and a venous pressure that was above the usual level of normality by the Moritz and von Tabora<sup>3</sup> method, but not much. I am inclined to regard 12 to 15 cm. as a high venous pressure in this man. He had a thick chest, so that one should probably add 5 to 6 cm. to the measurement.

DR. WHITE: What would you put as the top normal measurement according to your method?

DR. BURWELL: Using a zero point 10 cm. above the back, all our measurements in normal persons were under 15 cm., and 90 per cent of them were under 13 cm.

DR. WHITE: These readings are doubtless higher than those one would obtain with the subject in the vertical position. Twelve to fifteen centimeters is actually greater than the distance from the level of the clavicle to where the superior vena cava enters the right auricle; so I think that your readings may be too high from the standpoint of the actual or true venous pressures.

DR. BURWELL: Yes, but the arm-vein pressure is sensibly higher than the auricular pressure. If one takes 100 normal people and measures the venous pressures with the Moritz and von Tabora method, with the zero point 5 cm. down from the sternum, and charts them against the anteroposterior diameters of the chest, one gets, in general, a good correlation. The bigger the chest, the lower the venous pressure. If one charts the venous pressures determined by using the zero point 10 cm. from the back against the diameters of the chest, there is no correlation. It is an important point.

I am satisfied that this man had a high venous pressure. That is what I wanted to be sure of.

DR. WHITE: The neck veins were engorged.

DR. BURWELL: It is true that there is a statement about distended, pulsating neck veins that col-



no widening in that area, but this film was taken to bring out the right border.

The shadow in the lower part of the left chest is obviously fluid. In the films taken sixteen days later, one can see that the fluid has largely disappeared, although not completely.

DR. BURWELL: Do you see any evidence of calcification in the region of the heart?

DR. HOLMES: No. As you pointed out, I do not believe that the patient had enough scoliosis or emphysema to account for any of these things. I suppose that these calcified lymph nodes around the root of the lung are of some interest if one is thinking of tuberculous pericarditis. There is evidence that he had had a tuberculous infection at some time.

DR. BURWELL: The lungs are singularly clear.

DR. HOLMES: Yes, with the exception of this fluid. The interlobar fissure is visible, but I do not believe that it means anything. It may mean that the films were taken at exactly the right tilt.

DR. BURWELL: That is helpful to me.

Dr. White, with his characteristic precision, has recently studied the size of the heart in constrictive pericarditis. Many workers were entranced with the thought that here was a situation where one could observe severe evidence of cardiac failure with a normal-sized heart, and placed considerable emphasis on this point. But being a systematic kind of fellow, Dr. White set out to see how many of his patients with constrictive pericarditis had an enlarged heart, and it came out that 40 per cent had appreciable enlargement. Therefore, the fact that this heart was enlarged does not rule out constrictive pericarditis. But enlargement of this degree is unusual in constrictive pericarditis, not many of anybody's cases having had this much. Therefore one again gets a warning signal.

In favor of constrictive pericarditis is the fact that there is no other obvious explanation for this man's heart failure, except one to which I shall refer in a moment. He had no evidence of valvular disease, no evidence or history of hypertension and no evidence of congenital heart disease that I can find, and in so far as the evidence of these things is missing he falls into the type of persons who might have constriction. He had one other suggestive thing, namely, thick radial arteries. He had no pulsations in his feet and he had a complex electrocardiogram, and the question arises whether this man has to be classified on the basis of vascular degeneration of the myocardium. I allowed the pleasant thought of coarctation to pass through my mind when I read about the feet, but he had no hypertension or other things that go with coarctation and I see no great notches in his ribs, no collaterals and so forth, so that we can lay coarctation aside.

Could he have had some rare kind of occlusive arterial disease that shut off the arteries of the feet

and filled with the action of the heart, but it does not say what position the man was in when that was observed and I wanted a little reassurance. I think the question of venous pressure is an all-important one.

There is an interesting variety of cardiac disorder, associated with severe kyphoscoliosis, that is called "pulmonocardiac failure." This was admirably described by Chapman, Dill and Graybiel a few years ago. The disability is largely one of ventilation, and the involvement of the heart in the position of that picture is relatively small. Here is a man with slight scoliosis, and he may have had some limitation of excursion because of the relative immobility of the chest, but I do not believe that he had heart failure on the basis of the chest deformity, nor do I believe that all the symptoms can be explained on the basis of emphysema, some fixation of the ribs and loss of elasticity of the lungs, although all of these were probably present.

In considering some of the matters that have been tossed up with regard to the varieties of heart disease leading to obstruction or right ventricular failure, two important observations are that the heart was considerably enlarged and that the enlargement was not associated with a great reduction in excursion. An interesting question immediately comes to mind. In the x-ray and fluoroscopic examinations the amplitude of pulsation is said to have been within normal limits. The amplitude of the heart excursion is most closely related to the amount of blood that it expels per beat, and the amount of blood expelled with each beat has an important relation to the rate of the heart. He maintained a cardiac output of 4 liters per minute. The heart does not have to expel as much per beat if beating at a rate of 100 as it would if it were beating at a rate of 50, and the excursion would be smaller at a rate of 100. I should like to know if this excursion was normal for a rate of 50 or normal for a rate of 80.

DR. HOLMES: You have raised an interesting point, and one that I cannot answer. I do not believe that radiologists, at least those in this hospital, pay that much attention to that as they might. When the radiologist observes the heart with the possibility of an adherent pericardium in mind, he notes whether or not the amplitude of the beat is diminished, regardless of the pulse rate.

This heart is somewhat triangular in shape, which is slightly in favor of an adherent pericardium.

DR. BURWELL: The landmarks are not striking. It is rather an expressionless kind of heart silhouette.

DR. HOLMES: There is another point, if one can be certain about it; namely, one cannot distinguish the auricle from the ventricle along the left border. This is a difficult observation, particularly in a patient with fluid in the chest. It is not well seen. With an adherent pericardium or pericarditis with effusion, there is usually widening of the mediastinal shadow above the heart. This man certainly has

without giving symptoms of interference with the arteries in the myocardium and without causing local symptoms? I think that is unlikely.

I want to talk briefly about the confusing electrocardiograms. There are certain things that are entirely compatible with chronic pericardial disease. The characteristic things in constrictive pericarditis are low voltage and flat T waves. He had both of these, but he had some other things that are suggestive of anterior infarction. There was a slightly elevated ST, and an absent R in the precordial leads, with a variation in T waves in the precordial leads, which is also compatible with anterior infarction. The T waves in the limb leads are not like those of anterior infarction, and the low voltage is much more like pericardial disease than coronary disease in its unanimity in all the leads. I am not at all sure that a good thick layer of something over the myocardium would not interfere with the electrical activity in much the same way that an area of dead muscle in the same position would. I do not see any theoretical reason why a pericardial scar would not imitate an anterior infarction from that point of view. Also, as you well know, one of the characteristics about tuberculous pericarditis is that it is always accompanied by subpericardial myocarditis of varying degree and extent, and this may also lead to abnormal electrocardiographic manifestations. I am therefore inclined to find a good many difficulties in pinning a diagnosis of active coronary disease or of significant coronary occlusion on this man. There was no pain to suggest it, and not the fluctuation in the course that is usually produced by successive occlusions, and I think that the electrocardiogram can perhaps be explained on another basis.

I should like to introduce a discordant note and suggest that perhaps the whole picture was caused by cirrhosis of the liver. He had a number of things that go with cirrhosis of the liver. He had a big liver, a low protein and atrophic skin. On the other hand, he had no ascites, no varices and no spider telangiectases. He had had this thing too long, I believe, without ascites for it to have been cirrhosis of important degree. Moreover, although he had an enlarged spleen, I think that this and the increase in connective tissue in the liver were probably secondary to cardiac congestion and not to a primary cirrhotic process. The hypoproteinemia is rather important in the business of producing his symptoms, because when one has a total protein of 4.4 gm. the chances are that the albumin is severely reduced. The osmotic pressure is correspondingly reduced, and the transference of fluid to tissues is greatly facilitated. Under these circumstances a relative, slight increase in venous pressure may be important in causing edema, and I suspect that, so far as the edema goes, this man's low protein was quite as contributory as the dynamic situation created by his increased venous pressure.

I shall therefore make a diagnosis of constrictive pericarditis in this man, in spite of several points against it and in spite of the fact that not one of the usual cardinal signs was present. He had no evidence of calcium in the pericardium, he had no pulsus paradoxus, he had no ascites, although he had had congestion for three years, and his heart was certainly on the big side. I think more of the findings can be explained by constrictive pericarditis than by anything else. My second choice is localized arterial disease of the right ventricle, with myocardial degeneration, but I think that is a poor second, and I shall rest the case on constrictive pericarditis. If it was that, it was probably due to tuberculosis.

DR. WHITE: Dr. Burwell saw this patient during life but doubtless does not remember him. The note that he wrote at that time is certainly consistent with what he has just said. In December, 1943, he wrote:

This man has had fixed congestion for about one and a half years, preceded by intermittent congestion for a year. He exhibits distended veins, a feeble apex beat and a small pulse pressure (105/80) in spite of a rate of 48. He has no evidence of valvular disease. He has a large liver and edema. The lung descends in front of the heart. The chest moves in a limited way (vital capacity, 1500 cc.), and there is fluid and probably fibrous pleuritis at the left base. I believe that he has a constrictive pericarditis and that operation is justified. It is possible for extensive myocardial disease to produce the same picture, but I see no evidence of it. Two problems must be considered in the postoperative course—the low protein in the blood and the limited vital capacity. Removal of the pleural fluid would help the latter. Fluoroscopically the impressive things are a moderate increase in heart size and a marked limitation in the movement (excursion) of the heart in spite of the slow rate.

We both examined the patient fluoroscopically, if you recall.

DR. BURWELL: I begin to remember him, but I do not recall what fluoroscopy showed.

DR. WHITE: It seemed to us that he had a large heart that was somewhat limited in excursion. I asked you to come down because I wanted moral support for surgical exploration on account of the possibility of constrictive pericarditis. As a matter of fact, I do not remember exactly what I said myself at that time. Is there a note by me?

DR. WHEELER: We agreed essentially with Dr. Burwell that the case was not characteristic of constrictive pericarditis but that no other good diagnosis could be made. We thought that the man deserved a chance of help by operation.

#### CLINICAL DIAGNOSIS

Constrictive pericarditis (? type).  
Heart disease of other nature?

#### DR. BURWELL'S DIAGNOSIS

Constrictive pericarditis.

#### ANATOMICAL DIAGNOSIS

No evidence of constrictive pericarditis.

PATHOLOGICAL DISCUSSION

Dr. BEYJAMIN CASTLEMAN: An exploratory thoracotomy, performed by Dr. Sweet on the twenty-fourth hospital day, revealed 100 cc. of clear, straw-colored fluid in the pericardial sac. The sac was not thickened, and no adhesions were present. The pericardial fluid proved to be negative for tubercle bacilli on guinea-pig inoculation. Following the operation the patient continued as before, with periods of congestion relieved periodically by diuretics, and he was discharged on the forty-first hospital day.

We shall now continue with this patient's second admission, Dr. Burwell, and give you another chance.

Dr. Burwell: That is wonderful. Opportunity is supposed to knock but once.

ADDITIONAL HISTORY

Second admission (six months later). Following discharge the patient seemed somewhat improved and remained up and around on a regimen of limited fluids, digitals, ammonium chloride and periodic courses of mercurial diuretics. He complained of occasional mild pains and aches in the right shoulder, elbow and fingers, apparently unassociated with fever. He also noted an aching pain, occasionally sharp, over the region of the precordial incision, without radiation or relation to exertion; it did not respond well to morphine. About six weeks prior to admission he became rather suddenly worse, with increased congestion in spite of diuretics; he was confined to bed, and several chest taps were performed. His appetite became poor, and he lost considerable weight. One week before admission he suddenly developed a severe and persistent headache involving the right side of the head, with blurring of vision in the right eye and some weakness of the extremities on the left.

A further history revealed that a younger brother had had symptoms similar to those of the patient, including moderate enlargement of the heart, with auricular fibrillation, and hepatosplenomegaly. Physical examination showed a wasted man, with a large protuberant abdomen. There was no evidence of facial asymmetry. The neck veins were distended and pulsating. The heart and lung findings were essentially unchanged. The liver was felt five to six fingerbreadths below the costal margin, and there was questionable pulsation. The spleen was easily palpable. Marked pitting edema of the lower extremities was present, more so on the left. The left arm and leg were weaker than those on the right, the left abdominal reflexes were absent, and there were positive Babinski and Chaddock signs on the left.

The temperature was normal, and the pulse continued to range about 60. The blood pressure was unchanged.

FURTHER DISCUSSION

Dr. BURWELL: An initial spinal-fluid pressure of 290 mm. of water is not significant of what is going on in the central nervous system unless we know the venous pressure, because the former rises precisely with the latter.

This man had three things: a continuation of heart failure, pain in the right shoulder, elbow and fingers and over the precordial incision and some sort of intracranial accident that involved the motor tract on the right and caused a defect in the visual field of the right eye. The only way I can put these together as an alternative to the pericarditis that he did not have is in terms of vascular disease with thrombosis. He had a brother who had had similar symptoms. It was certainly not Wilson's disease. I do not find any way of explaining the cardiac situation on a neoplastic basis; we are fairly sure that he did not have a neoplasm of the pericardium, and there is no reason to think that he had an intracardiac neoplasm. Intracardiac neoplasm tends to be more progressive than this. I am inclined to believe that both the heart failure and the later symptoms were vascular in origin.

Dr. CASTLEMAN: By that do you mean infarction of the myocardium?

DR. BURWELL: I mean old infarction of the myocardium, probably multiple ones, with a degenerated myocardium based on cardiac disease (myomalacia).

DR. HOLMES: It may be of help to look at the later films. The heart has not changed in size or shape during the interval, but the patient has developed fluid in the right pleural space as well as in the left. The pleural fluid is persistent.

DR. BURWELL: It certainly is persistent. There is no evidence of an infectious process that would satisfy me. I find it difficult to diagnose tuberculosis of the pleura. The patient had had fluid in the pleura for many years, and that is not the way an active tuberculous lesion of the pleura is apt to do. The possibility of neoplasm in any queer situation is always good. He had a low serum protein, which means that fluid would pour out into the pleural cavity with great ease from slight inflammation or from slight elevation of the venous pressure. I am trying to think of a good alternative in terms of a noncardiac situation in his pleura, but he had so much evidence of injury to the heart in the electrocardiogram and in the size of the heart that I am inclined to believe that the edema, the pleural effusion and the dyspnea on exertion were cardiovascular in origin. I do not believe that he had beriberi, and there is no reason to believe that he had an aortic dissection. I doubt that the queer kinds of heart disease, such as scleroderma, play any role here. I am afraid I cannot do better.

DR. J. H. MEANS: Could he have had a process, not constrictive pericarditis, that constricted the inferior vena cava?

DR. BURWELL: That is an attractive suggestion, but such cases are extremely rare. This man had a high venous pressure in the arms; he should therefore have had something wrong with his heart rather than a localized difficulty.

DR. WHITE: Yes; isolated constriction of the inferior vena cava would protect the heart and prevent an increase in the venous pressure in the arms and neck. It would give a big liver, of course.

DR. MEANS: Was there a mediastinal process?

DR. BURWELL: That is what I was thinking of, an intracardiac tumor where the cava enters, thus plugging up the auricles. I should think that the heart would be smaller, underworked rather than overworked.

DR. WHITE: May I summarize the situation as I recall it? We had Dr. Burwell come down here to see this man because we were frankly puzzled. The patient did not run true to form respecting chronic constrictive pericarditis, but we thought it only right to explore and Dr. Burwell agreed.

After the operation I entered the following note:

This patient's condition in all its details is unique in our experience, although it resembles somewhat that of one other patient, in that right ventricular enlargement, dilatation and failure are present, unexplained by history, symptoms, signs, laboratory data or even operation. Whether myocarditis, toxic or infectious, or a bizarre

coronary heart disease involving primarily the auricles and right ventricle is the etiologic factor we have no way of determining. Certainly the treatment should consist of tonic therapy for the heart and diuretic therapy for the congestion. It is conceivable that, with time and the subsidence, spontaneous or otherwise, of the toxic or infectious factor, the right ventricle may regain its tone, but it probably will not do so.

When the patient came to us at the time of the last admission we still had no answer concerning the underlying etiologic factor in his case. I wrote:

It is possible that a constitutional disease, as suggested by Dr. William Beckman, — for example, dermatomyositis involving the myocardium as well as the other muscles of the body, — may be the answer, but it is simply conjectural at present. I favor further studies along this line. The patient feels a little better.

It was because of Dr. Beckman's suggestion that a muscle biopsy was done. This gave negative results.

DR. BURWELL: Constitutional disease is a good idea, but I should be inclined to think that a man of forty-three who had thick vessels and absent pulsations in the feet, with subsequent hemiplegia, would be likelier to have a vascular disorder, either a precocious form of arteriosclerosis or polyarteritis. The story certainly does not sound like polyarteritis, although that is possible.

DR. WHITE: Do you think that the cerebral lesion might have been the result of embolism?

DR. BURWELL: Yes, it could have been; but I find little evidence for subacute endocarditis. If he had an embolus, it must have come from a mural thrombus.

DR. MEANS: Does periarteritis nodosa produce anything like this?

DR. CASTLEMAN: It can mimic anything.

DR. BURWELL: There is one other point regarding constitutional disease. The patient had a reasonably low white-cell count with a high percentage of monocytes, and perhaps one ought to think of some more active form of tuberculosis. But I do not see any other good evidence of active tuberculosis and am inclined to think that all his difficulties were on a vascular basis. I do not believe that he had syphilis.

#### CLINICAL DIAGNOSES

Cardiac hypertrophy, cause unknown.

Congestive failure.

Acute pulmonary edema.

#### DR. BURWELL'S DIAGNOSIS

Myocardial degeneration based on vascular disease.

#### ANATOMICAL DIAGNOSIS

Interstitial myocarditis.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy showed a terminal bronchopneumonia and rather severe edema of the

lungs; there was also some fluid in both pleural cavities. The heart was enlarged but not markedly so; this was due mostly to dilatation rather than to hypertrophy. Since the heart weighed only 340

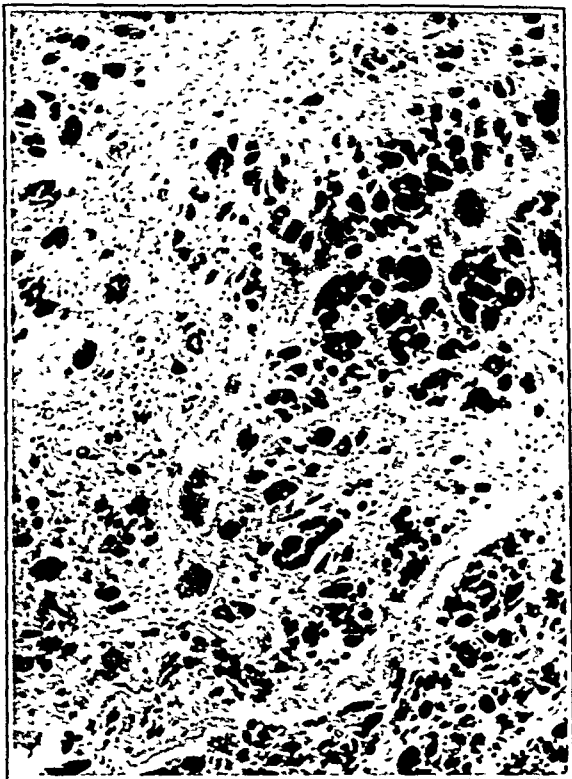


FIGURE 2. Photomicrograph of Heart Muscle.

gm., some might consider it to be at the upper limit of normal. The dilatation was equal in both the right and left chambers. The valves were negative. The coronary arteries were smooth, pliable and widely patent, and showed only a few atheromatous plaques. A small mural thrombus was found in the left auricular appendage, but no thrombi were detected in the other chambers of the heart. The heart itself was quite flabby, and the myocardium of both the right and left ventricles was rather gray in color, especially the trabeculae carneae and some of the papillary muscles. The liver was small, weighing only 1100 gm., and showed no evidence of cirrhosis. The spleen was small, weighing 160 gm., and contained two or three healed infarcts; it is quite possible that at one time the spleen was larger. One of the kidneys also had several healed infarcts.

Sections of the heart showed microscopically an unusual condition, which I am at a loss to explain. There was a diffuse interstitial fibrous myocarditis, involving both the right and left chambers but slightly more marked on the right (Figs. 2 and 3). Fibrous connective tissue had replaced a large amount of heart muscle, but its presence around in-



FIGURE 3. Photomicrograph of Heart Muscle (higher magnification).

Dr. WHITE: Could this be a residual from some such condition as was found in a case I discussed at a recent clinicopathological conference at the Peter Bent Brigham, a case of fatal influenza myocarditis? Such is doubtless rare when of high degree, but it is possible that we are failing to recognize a few

Dr. BURWELL: The patient did not have the circulatory picture of beriberi, low pulse pressure, a low circulation time, and no complications to go with it.

Dr. CASTLEMAN: Any acute infection that he had years ago that involved the myocardium could have produced this picture in the healed stage. Dr. BURWELL: The patient did not have vascular disease. The arteries were fairly good. The absent

cases of serious myocardial involvement following influenza or other virus diseases.

pulsations in the feet were not borne out by anything that was found.

DR. CASTLEMAN: The aorta was normal.

DR. WHITE: In a recent article, Levy and von Glahn,<sup>6</sup> of New York City, review a series of cases of myocardial disease of unknown cause. There are certain aspects of this case of ours that are somewhat similar to those of some of their group.

DR. MEANS: Dr. Castleman said that our patient had no hypertrophy.

DR. CASTLEMAN: I doubt that it fits in their group. I should rather believe that it was a deficiency affair or the end result of an acute infection years ago.

DR. MEANS: What about diphtheria? Does that end up with anything of this sort?

DR. CASTLEMAN: I believe that the myocarditis would be more spotty.

DR. BURWELL: What did you find in the brain?

DR. CASTLEMAN: Nothing was observed grossly or microscopically.

DR. WHITE: A word about the electrocardiogram. The low voltage of all the complexes in the limb leads is the most extreme that I have ever seen. The chest leads also indicate widespread myocardial disease.

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## THE STRAYER SURVEY AS IT CONCERNS SCHOOL HEALTH IN BOSTON

The recently published Strayer survey of the Boston public schools is having its repercussions, and it is to be hoped that some definite improvements may be accomplished before the echoes die away. Surveys in themselves are excellent, but they are chiefly fact-finding and oblivion is their usual fate unless some agency or agencies take on the responsibility of following through with the recommendations.

Physicians should be particularly interested in the section of the report that deals with health services and health and physical education, and its criticism of health education has already received

Three main faults, in particular, are to be found with health instruction in the Boston schools, but these three are fundamental. According to the report, "The teachers are not trained in this subject, or only partly trained, or in some cases badly trained; textbooks and other vital teaching aids are lacking; and there is no adequate curriculum." Health service, as another factor in health education, although furnished by competent physicians and a staff of excellent nurses, with an advisory committee of high caliber, suffers from overdetailed legal prescriptions and inferior physical equipment. All health-service activity is authorized by law: the school physicians, for example, are required separately and carefully to examine every child in their respective districts at least once in every school year and to send a written notice of any defect or disability requiring treatment to the parent or guardian. The result is a burden of rapidly performed and superficial annual physical examinations, whereas careful examinations performed once in three years would be of incalculably greater value. The present system may be considered to be antiquated and inadequate.

The functions and purposes of physical education are largely misunderstood. Thus, in a school document presenting a course in physical education it is stated that the purpose is to "provide an invigorating change from seat work." Four basic functions of physical education are given: to ensure the whole-some development of the vital organs of children; to teach functional skills; to develop and maintain an interest in various forms of motor activity; and to assist in the development of standard ways of behaving. Physical educators enjoy the reputation of having an aggressive attitude toward life, and in various instances have assumed or have been given the responsibility for health instruction, for which they are not trained, in addition to that for physical education.

Trained personnel, nevertheless, stands out as the greatest need in health instruction. The duty

\*Editorial. Health education in Boston schools. *J. A. M. A.* 126:1086, 1944.

editorial comment in the *Journal of the American Medical Association*\*—it is not that this phase of Boston's school activities is good, so much as it is that other cities may be no better.

usually falls to the lot of the room teacher. If she is not trained for this part of her job, it is up to the teachers' colleges of this health-minded nation to see that teachers of the future are so trained, just as it should be the responsibility of the medical schools to see that medical students are taught to understand and appreciate the duty that medicine owes to the school child.

In Massachusetts, well-organized and well-staffed state departments of Health and of Education have been engaged in the mutual enterprise of offering constructive health-education programs for the cities, towns and villages outside of Boston that care to participate. A joint committee in 1941 and 1942 made a study of health instruction in the secondary schools, and a relatively permanent joint steering committee has prepared courses of study for the various grades. The departments function largely in an advisory capacity and have, unfortunately, had difficulty in obtaining sufficient funds from the Commission on Administration and Finance to carry on these activities. The revised *Guide to School Health*, for instance, went to the commission on August 23, 1944, but as yet no action has been taken.

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#### THE MEDICAL CLASSIFICATION SCHEME OF THE BOSTON MEDICAL LIBRARY

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The chief disadvantage of the Boston Medical Library scheme has been its infrequent revision, with lack of sufficient expansion in certain sections. These criticisms have been met in the 1944 edition, and in addition to the usual schedules, Mr. Ballard



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REFERENCES

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CORRESPONDENCE  
DETERTERIOUS EFFECTS OF PRIVINE  
HYDROCHLORIDE

*To the Editor:* Privine hydrochloride, as 0.10 and 0.05 per cent solutions, was introduced in 1942 as a nasal vasoconstrictor. The advantages claimed for Privine were prolonged vasoconstriction, small dosage and physiologic rationale. The dose of Privine is two to three drops nasally, and it produces symptomatic relief from the nasal congestion for two to six hours. Since it is prepared in isotonic solution buffered to the same pH as that of the "delicate nasal mucous membranes," it was said to be nonirritating; furthermore, it was claimed that it restores the alkaline pathologic secretions to the normal acid range. Almost overnight Privine became the popular nose drop. During the last year I sensed the fact that more and more patients were becoming chronic users of Privine and began to see a number of patients who had either marked vasomotor reactions superimposed on the course of hay fever or definite exacerbations of symptoms in cases of typical hyperplastic vasomotor rhinitis. These patients generally gave a similar story. "Privine was prescribed either for a 'head cold' or for some form of allergic coryza. At the beginning they found that one to two drops of Privine instilled nasally gave excellent relief for two to six hours. In fact the majority thought this was the best nose drop they had ever used. As the patients continued to use the medication, however, they found that the nasal congestion began to recur as often as every one or two hours. Some soon began to believe that they could not get along without the use of Privine and would take out a vial to show that they kept it with them at all times."

A frequent observation following the use of Privine for hay fever was the continuance of symptoms far beyond the pollinating season. This was most unusual and was commented on by a number of "Privine addicts." In many cases the Privine had not been prescribed by a physician. For example

STANDARDS OF MEDICAL EDUCATION

*To the Editor:* I have read with interest the editorial "Standards of Medical Education," which appeared in the February 1 issue of the *Journal*. May I comment on it, as it shows some lacunae which the medical profession may wish to have filled, and some errors in statement of fact which, while not of vital import, should be corrected in the interests of accuracy.

The editorial does not do justice to the Approving Authority in saying that "the failure of the Massachusetts Approving Authority to accredit the Middlesex University School of Medicine was upheld by the Superior Court of Suffolk County." The failure on the part of the Approving Authority, if there was any failure, would be in the procedure leading to the actual decision and not in the omission of a decision, as the writer of the editorial implies. A definite decision was made, with full knowledge that the decision meant, as far as the Approving Authority was concerned, that a medical school which had been growing vigorously and improving itself rapidly, with a faculty and students, and with property and equipment estimated at one and a quarter million dollars, book value, would be closed at a time when the national need for more physicians is urgent.

The denning of the personal references in the editorial is not entirely clear, but in the spring of 1935 the secretary of the Massachusetts Medical Society informed me as secretary of the Board of Registration in Medicine that the president of the Society, a past-president and he himself, having been advised by a high political authority, were opposed to the introduction, for the 1936 session of the Legislature, of a bill to exercise some control over medical education, and he urged that no bill be introduced. The matter was considered by the Board at one of its meetings, and, notwithstanding the objection by the officers of the Society, the Board introduced a bill which, however, cannot be recognized in the Act of 1936.

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I believe that Privine should never be used for longer than four to five days and then only when the patient is under the care of a physician. Furthermore, something should be done about the indiscriminate sale of Privine over the drug-store counter.

520 Beacon Street  
Boston 15  
LIVING W. SCHILLER, M.D.

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obvious, there remains to be discussed, first, what the law does or does not say, and second, what the law does or does not mean. I can only touch on some of these points.

At least three defects of the law are evident at once. As Judge Cabot said, "The statute lays down neither for the Approving Authority nor this court any guide by which approval should be granted or withheld."

A second defect is that if approval is once given, it cannot be taken away. No matter how much the school may deteriorate, the Approving Authority can only sit by and let it go downhill, with approval. This would put the Approving Authority in a ridiculous position.

A third defect is that if a school meets the requirements 90 per cent, the law provides for no status intermediate between approved and not approved. Such status does in fact exist, namely, "on probation," although it is not recognized by the statute. In the requirements for approval drawn up by the Approving Authority in 1936, an attempted make-shift for the solution of the problem caused by this defect was introduced by using the word "adequate" in eight of the seventeen requirements. A school may be adequate in giving a good medical education, although inadequate in one or more of its departments. Few schools satisfy even themselves in every respect.

When the question was raised as to whether the make-shift solution would be satisfactory, a bill was introduced before the Legislature to cover this very point but it was not enacted. Yet right here is perhaps the most serious defect in a very defective law.

The writer of the editorial is too optimistic in saying "At long last the practice of medicine in the Commonwealth is open only to the men and women who have been properly trained and Massachusetts need no longer be called 'the dumping ground for medical-school graduates'." Apparently a clerical error has slipped in here as since about 1914, only medical-school graduates have been admitted to examination. But the writer has forgotten that every physician who matriculated in a medical school before January 1, 1941, no matter how long before, is eligible for admission to examination, even if the medical school from which he graduated has never been approved.

On the other hand, the writer of the editorial is too pessimistic. Referring to bills now before the Legislature, he says, "The passage of such legislation can either halt or stop forever the progress toward higher medical standards." "Forever" is a long time. Does he think that the General Court of Massachusetts can, in 1945, take any action that will last forever? Then he goes on to say, "and high standards of medical education *must* be maintained in these days when the practice of medicine is being subjected to criticism." *Must* they be maintained? Let him see the Army about that and then talk with some of the persons in medical education who are vocal on this subject, such as Dean Branch, Dr. Everts Graham, Dr. Victor Johnson, Dean MacEwen, Dean Rappleye and Dr. Joseph Wearn, and see if what *must* be done *has been* done.

The many defects of the Act of 1936, Chapter 247, I shall take up at another time, for they are serious and should be remedied. Some of the bills which have been introduced incorporate suggestions for improvement. There is needed a discriminating understanding of what the situation demands. We are in the transition period of a reform, and every reform presents the possibility of at least two dangers — first, from fanatical reformers who ruthlessly seek the desired end without regard for the harm they may do on the way, and second, from the self-seeking who may profit from the reform and to whom justice is meaningless as applied to persons other than themselves. Against both dangers we should be on guard now.

STEPHEN RUSHMORE

520 Commonwealth Avenue  
Boston

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The *Journal* is primarily interested in the improvement of standards of medical education in Massachusetts, rather than whether or not this or that medical school should be accredited. Few will deny that in 1936, by virtue of its inadequate medical-practice act, the Commonwealth had become a "dumping ground for the graduates" of non-approved medical schools. Certainly those who are responsible for the health of the people should undergo a course of

training that meets certain minimum standards, and the creation of the Approving Authority was a step in the proper direction. It is to be hoped that future legislation will continue forward rather than turn backward. — Ed.

## NOTICES

### NORTON MEDICAL AWARD FOR 1946

The Norton Medical Award, which is offered annually by W. W. Norton and Company, Incorporated, to encourage the writing of books on medicine and the medical profession for the layman, totals \$3500 (\$1000 outright and the balance an advance against royalties). The author must be a professional worker in the field of medicine, or a collaborator with such a person. The final date for submission of manuscripts is December 1, 1945. Further details are contained in a descriptive circular that may be obtained from W. W. Norton and Company, Incorporated, 70 Fifth Avenue, New York 11, New York.

### BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in the Main Lecture Room of the Harvard Biological Laboratories on Wednesday, March 21, at 8 p.m.

#### PROGRAM

- Estrogen Metabolism in Women. Drs. O. W. Smith and G. Van S. Smith.
- Vitamins in Relation to Skeleton Growth. Dr. S. B. Wolbach.
- Chorionic Luteotropin and Luteal Function in Monkeys. Dr. F. S. Hisaw.

### GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Wednesday, March 21, at 8:15 p.m. Dr. Philip Levine will speak on the subject "The Clinical Significance of the Rh Factor." A discussion by Drs. Benjamin Alexander, William Dameshek and Karl Singer will follow.

### NEW YORK INSTITUTE OF CLINICAL ORAL PATHOLOGY

The New York Institute of Clinical Oral Pathology will hold an open meeting at the New York Academy of Medicine, 2 East 103rd Street, New York City, on Monday, April 30, at 8:15 p.m. A symposium entitled "A Survey of the Antibiotic Problem" will be presented. The program is as follows:

- The Role of Biotics and Antibiotics in Chemotherapy. Dr. Daniel Laszlo.
- The Problem of Penicillin in Treatment of Mixed Infections. Dr. Frank Lamont Meleney.
- The Treatment of Acute and Chronic Infections of the Jaws with Antibiotics. Dr. Leo Stern.
- The Relative Value of Antibiotics in the Treatment of Otolaryngic Diseases. Lt. Col. Kenneth M. Kahn.
- Evaluation of Antibiotic Agents for Root Canal Treatment. Dr. Louis I. Grossman.
- The Role of Iontophoresis in Ocular Therapy with Antibiotics. Dr. Ludwig von Sallmann.
- Treatment of Ulcerative Stomatitis (Vincent's Infection) with Penicillin. Dr. Alvin E. Stroock.

For further information all communications should be addressed to G. Roistacher, Executive Secretary, 101 East 79th Street, New York 21, New York.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 22

##### FRIDAY, MARCH 23

- \*9:00-10:00 a.m. Some Aspects of Cardiac Surgery. Dr. Robert E. Gross. Joseph H. Pratt Diagnostic Hospital.
- \*9:00-10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.
- 10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Mallory Building, Boston City Hospital.

(Notices continued on page xvii)

# The New England Journal of Medicine

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Volume 232

MARCH 22, 1945

Number 12

## THE TREATMENT OF URETERS INJURED DURING GYNÉCOLOGIC OPERATIONS

FRANCIS M. INGERSOLL, M.D.,\* AND JOE V. MEIGS, M.D.†

BOSTON

**ACCIDENTAL** injury of a ureter is the most frequent serious complication of gynecologic pelvic operations. This fact was brought to our attention by the occurrence of 7 ureteral injuries in 590 total hysterectomies and 1 ureteral injury in 170 supravaginal hysterectomies done during a five-year period at the Massachusetts General Hospital. These 8 cases will serve to illustrate the type of injuries that occur and the surgical principles and procedures to be followed in repairing them.

### PRINCIPLES OF TREATMENT

#### *The Incised or Ligated Ureter*

#### TREATMENT AT TIME OF INJURY

Following the principle of repair at the time of the operation, an end-to-end anastomosis is indicated. The injured portion of the ureter is excised, and the two ends of the ureter are freed to provide adequate material, both proximally and distally, which to work. A nylon ureteral catheter is introduced up to the kidney pelvis and the distal end is placed in the bladder. The catheter should be partially drawn out during cystoscopy at the end of the operation and attached to the thigh. The two ends of the cut ureter are approximated by suturing them around the catheter by the use of mattress sutures of fine silk, cotton or catgut. The area of the anastomosis is drained retroperitoneally through a stab wound in the flank by means of an empty Miller wick.

Bump and Crowe<sup>1</sup> in 1929 reported on their experience with end-to-end ureteral anastomoses in dogs. They anastomosed over one catheter and decompressed the proximal ureter with another brought out through a stab wound in the flank. Without the catheters their anastomoses resulted in fistulas and hydronephrosis. Curtis<sup>2</sup> in 1929 reported a case with successful anastomosis by this method. Dr. Fletcher H. Colby, in a personal communication, has advised a proximal decompression of the ureter with a small rubber catheter, omitting the inlying ureteral catheter. Proximal decompression has not been used in our cases. Three of the 8 cases illustrate the treatment of the incised or ligated ureter. These are reported below.

**CASE 1.** G. P., a 47-year-old quartipara, had a fibroid uterus that had grown two thirds of the way to the umbilicus. At operation hemorrhage occurred from varices in the left broad ligament, and the ureter was clamped and cut 12 cm.

\*Assistant in gynecology, Harvard Medical School; assistant in surgery, Massachusetts General Hospital.  
†Clinical professor of gynecology, Harvard Medical School; chief, Vincent Memorial Hospital—the Gynecological Service, Massachusetts General Hospital.

a splint during the healing of the ureter and also or rubber ureteral catheter. The catheter serves as tomosis should be done over an indwelling nylon third important principle is that all ureteral anastomosis will be discussed later. The technique of ureter into the bowel or bladder. The technique of ureterostomy or transposition of the kidney may be accomplished by nephrostomy, skin ureterostomy or transposition of the kidney. Preservation of the remaining kidney is unwise. Preservation or nephrectomy without knowledge of the renal function, and the sacrifice of a kidney by ligation is not an adequate means of determining function of the other side can be determined. Partial function on the side of the injured ureter until the every effort should be made to preserve the kidney abscess and later came to nephrectomy. Secondly, fourth developed a urinary fistula and a pelvic tion in 4. Three of these patients did well; the reviewed herein, injury was noted at time of operation in 8 cases. In the 8 cases, round uncomplicated procedure. In the 8 cases, pituitary no longer than that required for the may result in a successful anastomosis, with hospitalization no longer than that required for the since proper treatment at the time of operation of the utmost importance. This is especially true of the immediate recognition of the injury is dealing with the problem of the damaged ureter. First, the importance of the problem of the damaged ureter. Important principles that should be observed when to the circumstances of the case, there are certain Although each patient must be treated according

from the bladder. Both ends of the ureter were freed and anastomosed end to end over a ureteral catheter. Five mattress sutures of silk were used. The area of the anastomosis was drained through a stab wound in the flank. The catheter came out on the 4th day, and urine drained from the flank wound for 6 days. A slight hydronephrosis was demonstrated by intravenous pyelogram but later disappeared. An intravenous pyelogram 1 year later was normal.

CASE 2. E. D., a 47-year-old primipara, had endometriosis involving the ovaries and the posterior cul-de-sac. The left ureter was injured as the uterine vessels were being tied during the course of a total hysterectomy and bilateral salpingo-oophorectomy. A sleeve type of anastomosis was done over an inlying catheter, the distal end being placed inside the proximal end and secured by arterial silk. The area was drained by an empty Miller wick through a stab wound in the flank. The catheter came out on the 4th day, resulting in a ureterovaginal fistula, which healed in 17 days. At that time a marked hydronephrosis was demonstrated by intravenous pyelogram, but within 6 weeks an intravenous pyelogram was normal.

CASE 3. E. D., a 41-year-old, unmarried woman, had a fibroid tumor the size of a 7-month pregnancy. During the hysterectomy the left ureter was ligated when the uterosacral ligaments were clamped and cut. The damaged ureter was freed, and the ligature removed. After the uterus had been removed a sleeve type of anastomosis was done, the distal end of the ureter being placed inside the proximal end and held in place with three No. 00 chromic-catgut stitches. A cuff of peritoneum was sutured around the site of the anastomosis. The area was drained retroperitoneally, the wick being brought out through the left flank. A ureteral catheter was not used. Urine drained copiously from the stab wound for 2 weeks. During the 3rd week after operation a large abscess, accompanied by pyelonephritis with chills and fever, developed in the left lower quadrant of the abdomen. Re-exploration 7 weeks later demonstrated that the upper end of the left ureter ended in the abscess cavity; the distal section was not identified. A left nephrectomy was performed, recovery from which was uneventful.

*Comment.* This case, the only one of the 3 reported that was done without a ureteral catheter, demonstrates the dangers and difficulties encountered when a ureteral catheter is not used.

### *The Resected Ureter*

Repair of the resected ureter is a problem. End-to-end anastomosis is usually impossible, so that one of the following methods must be used: ureterovesical transplant, ureterosigmoidal anastomosis, skin ureterostomy or ligation of the distal and proximal ends of the ureter. Nephrectomy must occasionally be resorted to.

*Ureterovesical transplant.* Ureterovesical transplant is the most satisfactory procedure. The cut end of the ureter is freed, the bladder is mobilized, and the free end is measured against the site of implantation to make certain that suturing is possible without tension on the ureter. To avoid strain resulting from bladder distention, a site as low as possible on the bladder should be chosen. An incision through the detrusor muscle and mucosa is made, and the ureter, which has been split for suturing, is brought through it into the bladder. The two flaps are then sutured to the bladder mucosa and the bladder muscle is closed about the ureter, one of the stitches catching the adventitia to help hold it in place. The bladder wall is then drawn about the ureter in such a way as to afford an oblique entrance into the bladder. The operative site is drained with

a Penrose drain. Bladder distention is avoided by using a suprapubic drain or an indwelling urethral catheter for as long as ten days following operation. This is a safe procedure if the ureter will reach the bladder without tension.

*Ureterosigmoidal anastomosis.* If the resection of the ureter has been high, ureterosigmoidal anastomosis may be indicated. This method of preserving kidney function is a difficult technical procedure and is frequently complicated by sepsis. It should not be attempted by the inexperienced surgeon, since skin ureterostomy is safer.

The technic of ureterosigmoidal anastomosis was standardized by Coffey<sup>3</sup> in 1928. There are many modifications of his method, but his principle of a valvelike action on the ureteral wall as it passes tangentially through the bowel wall is the important technical feature of the operation. The ureter is exposed and the sigmoid is brought over to it, the site of implantation being as low in the bowel as possible without tension. An incision 4 cm. long is made through the serosa of the bowel and through the muscularis to the submucosa, the latter being stripped from the muscularis over a small area so that the ureter will have a place to lie. The segment of bowel is clamped above and below with rubber-covered clamps. A tiny incision is made in the mucosa with a cautery at the lower end of the prepared area. A stitch is attached to the free end of the ureter, and the needle is passed through the mucosal incision along a grooved director. The needle and stitch are brought out through the bowel wall, and by traction the ureter is pulled within the sigmoid. The ureter is held by placing a stitch through the peritoneum and muscularis, which catches a small bit of ureteral wall. The muscularis and peritoneum are closed with interrupted catgut.

*Skin ureterostomy.* A simple procedure to preserve kidney function, and one that adds little to the operation, is skin ureterostomy. The sectioned ureter is freed above the injury. Care is taken to preserve the loose areola tissue around the ureter so as to maintain its blood supply. The lateral peritoneum is dissected free, and the ureter is brought out through a stab wound on the anterior abdominal wall at the level of and medial to the anterior superior spine. The ureter is not stitched to the peritoneum or fascia but is fastened to the skin.

*Ligation of ureter.* A fourth possibility in the care of resected ureter is ligation. If previous urologic studies have shown good function of both kidneys without infection, ligation is probably the quickest and easiest procedure, although the chance must be taken that aseptic necrosis will follow ligation. Barney<sup>4</sup> in 1912 demonstrated experimentally that not all ligated ureters result in an aseptic necrosis. Hepler<sup>5</sup> in 1940 found that 3 per cent of patients so treated died, 24 per cent developed urinary fistulas, and 15 per cent ultimately had to have nephrectomy. Peacock<sup>6</sup> in 1941 reported a series of 8 patients so

Another reason for nephrectomy for ureterovaginal fistula was found in Case 3, discussed above. This patient's left ureter was anastomosed end to end—unsuccessfully. There was profuse drainage of urine through the stab wound and some vaginal drainage. A pelvic abscess formed and was drained through the stab wound. Seven weeks after operation the patient was still seriously ill. There was a marked hydronephrosis as demonstrated by intravenous pyelogram, and the temperature reached 104°F. daily. Re-exploration demonstrated that the left ureter ended in the abscess cavity; the distal end was not identified. A nephrectomy was done and the pelvic sepsis subsided. Recovery was rapid and uneventful, and the patient was free of symptoms at the end of three months.

Some ureterovaginal fistulas develop late and are accompanied by relatively little sepsis. In this event, exploration of the site of the ureteral injury is indicated, and ureterovaginal transplantation is usually possible. This alternative is preferable to nephrectomy. Two cases, described below, were successfully treated in this manner.

Case 6. M. G., a 35-year-old nulliparous woman, had severe vaginal bleeding of 6 weeks' duration and an enlarged uterus. A total hysterectomy was done, and on the 15th postoperative day a fistula was noted and cystoscopy demonstrated a blocked ureter on the right side. One month later, exploration showed the right ureter to be involved in scar about 5 cm. from the bladder. A ureterovaginal transplant was done and the bladder was drained suprapubically. After operation an intravenous pyelogram demonstrated a slight hydronephrosis on the right; this subsequently subsided, and the patient was well 4 years after operation.

Case 7. A. H., a 49-year-old nulliparous woman had a supravaginal hysterectomy for the removal of a large fibroid in the right broad ligament. The operation was accomplished with some difficulty. A right ureterovaginal fistula developed on the 20th postoperative day, the block being 4 cm. from the ureteral orifice. Two months later, a ureterovaginal transplant was done, the dilated right ureter being implanted without undue tension. The convalescence was uneventful, and an intravenous pyelogram 4 months later showed good kidney function. Two years later the patient was still well.

If the site of the ureterovaginal fistula is high and at exploration the cut end of the ureter will not reach the bladder, ureterovaginal anastomosis should be considered. In cases in which the ureter is dilated and pyelonephritis is present, nephrectomy is a safer operation than ureterovaginal anastomosis, the latter being contraindicated in the presence of pyelonephritis.

There is still another type of injury not recognized at operation that should be mentioned, namely, the ligated ureter that does not cause a fistula. How many such cases there are is unknown. Newell<sup>17</sup> in 1939 reported 15 cases of ureteral injury; 6 of these patients had unilateral ligations that were unsuspected until discovery at autopsy.

All patients who have a difficult time after operation should be watched for ureteral difficulties. Severe costovertebral pain may be caused by a

treated, 2 of whom died as a result of fistula and sepsis. He advocates immediate nephrectomy, which may be safer than ligation.

The present series includes the following example of successful ligation.

Case 4. M. M., a 50-year-old bipara, was admitted because of an abdominal mass extending halfway to the umbilicus. At operation a large fibroid was found, with the left tube and ovary thinned out over the body of the tumor. The left ureter was in the posterior sheath of the broad ligament, and a large section was inadvertently excised. Both ends of the excised ureter were ligated and the total hysterectomy was completed. After operation the temperature rose daily to 101°F. but subsided on the 8th day. The urinary output was good. The nonprotein nitrogen rose to 44 mg. per 100 cc., but fell to 20 mg. on the 14th day. The patient was discharged on the 15th postoperative day and was well at follow-up 1 year later.

#### TREATMENT AFTER OPERATION

Recognition of ureteral injury after operation is a surgical as well as a urologic problem. The methods of meeting this complication should be known to both the surgeon and the gynecologist. Bilateral ligation may be diagnosed by anuria and a rising nonprotein nitrogen. Cystoscopy demonstrates the blocked ureters. For this reason, the urinary output of gynecologic patients should be carefully followed. Prompt relief of bilateral ureteral obstruction is necessary, and nephrostomy is the quickest and safest procedure. This drains the blocked kidneys and tides the patient over her acute difficulty. She can then be observed to see whether the catgut ties are dissolving, thus relieving the ureteral obstructions. Subsequent therapy depends on circumstances. Deligation may be attempted, but the operative mortality is high, and the risk of subjecting the patient to immediate postoperative re-exploration is unwarranted.

Injury to one ureter by ligature, unrecognized at the time of operation, is usually revealed by the development of a ureterovaginal fistula. These fistulas ordinarily appear ten days to three weeks after operation. Some of them close spontaneously, and such an event should be awaited; failing this, treatment must be considered. Sub-sidence of local inflammatory processes around the site of the fistula is necessary, since an attempt to close it before resolution will be futile. In elderly women with a ureterovaginal fistula together with sepsis, nephrectomy, although sacrificing the kidney, is both quick and safe. The following case in this series was so treated successfully.

Case 5. C. G., a 63-year-old unmarried woman, developed a ureterovaginal fistula following hysterectomy for endometrial cancer. During operation it was necessary to stop bleeding from the left corner of the vagina by a figure-eight suture. The fistula, which was first noticed on the 8th postoperative day, failed to close of its own accord. Considering the patient's age, her disease and the fact that the other kidney functioned well, a nephrectomy was done. The convalescence was satisfactory, and the patient has remained well for the 2 years during which she had been followed by the Tumor Clinic.



from the bladder. Both ends of the ureter were freed and anastomosed end to end over a ureteral catheter. Five mattress sutures of silk were used. The area of the anastomosis was drained through a stab wound in the flank. The catheter came out on the 4th day, and urine drained from the flank wound for 6 days. A slight hydronephrosis was demonstrated by intravenous pyelogram but later disappeared. An intravenous pyelogram 1 year later was normal.

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duration of symptoms was 5.1 years. As shown by Table 1, 157 patients (60 per cent) presented

Table 1. Duration of Symptoms in Patients Without Complications.

DURATION	No of Cases	PERCENTAGE
37	39	25
Less than 1 yr.	34	22
1-2	34	22
3-4	33	21
5-9	33	21
10 or more	23	15
Unknown	8	5
Total	157	

at operation no biliary disease other than gallstones. Their histories reveal that symptoms were present for as long as thirty-nine years, with the average period 4.6 years. It is significant that 34 per cent of the patients had symptoms for more than five years and 15 per cent for more than ten years.

One hundred and three patients (40 per cent) had one or more complications at operation, including acute cholecystitis, acute pancreatitis, cholecholelithiasis and carcinoma of the gall bladder (Table 2); of these, 6 had more than one complica-

Table 2. Duration of Symptoms in Patients With Complications.

DURATION	No of Cases	PERCENTAGE
37	36	33
Less than 1 yr.	15	14
1-2	17	15
3-4	17	15
5-9	3	3
10 or more	3	3
Total	109*	

\*6 patients listed twice, having had more than one complication

tion and are therefore listed twice. Whereas the average duration in the cases without complications was 4.6 years, it was 6.7 years in the cases with complications. Generally speaking, the longer the duration of symptoms of gallstones, the greater was the probability of complications. The interesting fact is that of this series 33 per cent had symptoms for less than one year before operation and 47 per cent for less than three years. Sixty-nine patients (27 per cent) had acute cholecystitis, including empyema, gangrene and acute free perforation of the gall bladder (Table 3). The

Table 3. Duration of Symptoms in Patients with Acute Cholecystitis.

DURATION	No of Cases	PERCENTAGE
37	23	33
Less than 1 yr.	18	26
1-2	12	17
3-4	12	17
5-9	24	35
10 or more	2	3
Unknown	2	3
Total	69	

toms for five or more years, 33 per cent had had symptoms for less than one year. Six had no symptoms before the acute attack precipitating operation. These figures correspond with those in an analysis by Glenn,<sup>7</sup> according to which 7 per cent of a series of patients had complications at the time of the initial symptoms and approximately 40 per cent thus apparent that acute cholecystitis may develop either early or late during the course of gallstones.

Although there is no general agreement concerning the pathogenesis of acute pancreatitis, a significant and fairly constant finding is its association with gallstones.<sup>8</sup> Calculi have been reported in 70 to 81 per cent of cases of acute pancreatitis,<sup>9</sup> which is therefore usually considered a complication of gallstones. In the present series 10 patients (4 per cent) had acute pancreatitis (Table 4). These cases,

Table 4. Duration of Symptoms in Patients with Acute Pancreatitis.

DURATION	No of Cases	PERCENTAGE
37	5	50
Less than 1 yr.	3	30
1-2	2	20
10 or more	10	
Total	10	

according to Abell's<sup>10</sup> classification, included acute pancreatic edema, acute pancreatic necrosis and acute pancreatitis with hemorrhage. Five patients in this group had symptoms for less than one year before operation, 2 having acute pancreatitis with their first attack of biliary distress; 3 had symptoms for two years and 2 for thirteen and seventeen years, respectively. The average duration was 3.9 years. Acute pancreatitis was often an early complication than a late sequelae of gallstones. Thirty-two patients (12 per cent) had stones in the common duct (Table 5). The average duration

Table 5. Duration of Symptoms in Patients with Cholecholelithiasis.

DURATION	No of Cases	PERCENTAGE
37	10	31
Less than 1 yr.	4	12
1-2	13	41
3-9	5	16
10 or more	32	
Total	32	

of symptoms was 5.6 years, which with the exception of the cases of carcinoma of the gall bladder was the longest for those with complications. The duration period varied from less than one year to twenty years, except for 1 case with symptoms for forty years. Ten patients (31 per cent) were operated on before the end of twelve months; in fact, 3 were found to have stones in the common duct at operation following the first attack of colic. Fifty

blocked ureter, and an intravenous pyelogram should be done in this event to prove or disprove the diagnosis. The following case is illustrative.

CASE 8. M. L., a 49-year-old nulliparous woman, had a total hysterectomy for fibroids. A daily temperature of 102°F. was attributed to a draining ear until she complained of costovertebral angle tenderness. An intravenous pyelogram demonstrated that the left ureter was blocked 5 cm. from the bladder. The patient's condition improved until the 20th postoperative day, when she lapsed into a coma and died. Autopsy showed that the left ureter was tied off by a catgut ligature; that was also a massive cerebral hemorrhage.

#### SUMMARY AND CONCLUSIONS

Eight cases of ureteral injury among 760 hysterectomies performed at the Massachusetts General Hospital are discussed.

The following conclusions are drawn: immediate recognition of the injury is essential; kidney function should be preserved whenever possible; all ureteral anastomoses should be done end to end over a ureteral catheter; bilateral ligation is best treated by bilateral nephrostomies; and ureterovaginal fistulas that do not close spontaneously should be repaired either by ureteral transplant to the bladder or bowel or by nephrectomy.

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## THE TIME FACTOR IN THE DEVELOPMENT OF COMPLICATIONS OF GALLSTONES\*

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IF GALLSTONES remain in the gall bladder, according to Cheever,<sup>1</sup> "sooner or later, if their host lives long enough, they will cause damage of a serious nature." With this statement there can be only general accord, but the phrase "sooner or later" is vague. The following statistical study was undertaken with the hope of establishing a more definite time relation between the original disease and the sequelae.

It is generally acknowledged that gallstones may exist for many years without giving rise to symptoms,<sup>2</sup> but once they have been demonstrated, one is obliged to assume that eventually such sequelae as acute cholecystitis, acute pancreatitis, common-duct stones and carcinoma of the gall bladder may develop. Acute cholecystitis and acute pancreatitis may occur when no stones are to be found in the gall bladder; stones may even occur in the common duct with no calculi present in the gall bladder. The complications and sequelae of cholelithiasis, however, cannot be anticipated if the existence of stones in the gall bladder has not been established. Accordingly, the time factor for the development of biliary complications must resolve itself into the

time lapse between the onset of primary symptoms or demonstration of stones and the clinical onset of these complications.

A better understanding of this time factor would be of great assistance in treating today's civilians. Gallstones, which are estimated to effect approximately one third of the adult population,<sup>3,4</sup> occur most frequently in persons over forty years old, and these are the people so essential on the home front. The older the age group, the higher is the incidence of gallstones. Lee has stated<sup>5</sup>: "Gallstones . . . increase in frequency with advancing birthdays, and it is likely that if people lived to be one hundred and twenty they all would have gallstones. Certainly, autopsies performed on people of eighty or over show almost uniformly the presence of gallstones." Moreover, as I<sup>6</sup> pointed out in a previous paper, operation for gallstones may have to be deferred during the war because of the shortage of nursing and professional services, hospital accommodations and domestic help to care for children, as well as the desire of workers to remain constantly on their jobs.

A study has therefore been made of 260 private records of operation for gallstones. The average

\*Presented at the Section of Surgery, American Medical Association, June 15, 1944

duration of symptoms was 5.1 years. As shown by Table 1, 157 patients (60 per cent) presented

TABLE 1. Duration of Symptoms in Patients Without Complications.

DURATION	No of Cases	PERCENTAGE
Less than 1 yr.	25	15.9
1-2	22	13.9
3-4	34	21.0
5-9	23	14.6
10 or more	30	19.0
Unknown	23	14.6
Total	157	

at operation no biliary disease other than gallstones. Their histories reveal that symptoms were present for as long as thirty-nine years, with the average period 4.6 years. It is significant that 34 per cent of the patients had symptoms for more than five years and 15 per cent for more than ten years.

One hundred and three patients (40 per cent) had one or more complications at operation, including acute cholecystitis, acute pancreatitis, cholecholelithiasis and carcinoma of the gall bladder (Table 2); of these, 6 had more than one complica-

TABLE 2. Duration of Symptoms in Patients With Complications.

DURATION	No of Cases	PERCENTAGE
Less than 1 yr.	36	22.2
1-2	15	9.4
3-4	38	23.8
5-9	17	10.6
10 or more	3	1.9
Total	109*	

\*6 patients listed twice, having had more than one complication

tion and are therefore listed twice. Whereas the average duration in the cases without complications was 4.6 years, it was 6.7 years in the cases with complications. Generally speaking, the longer the duration of symptoms of gallstones, the greater was the probability of complications. The interesting fact is that of this series 33 per cent had symptoms for less than one year before operation and 47 per cent for less than three years. Sixty-nine patients (27 per cent) had acute cholecystitis, including empyema, gangrene and acute free perforation of the gall bladder (Table 3). The

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DURATION	No of Cases	PERCENTAGE
Less than 1 yr.	23	33.3
1-2	8	12.0
3-4	12	17.7
5 or more	24	35.3
Unknown	2	3.0
Total	69	

toms for five or more years, 33 per cent had had symptoms for less than one year. Six had no symptoms before the acute attack precipitating operation. These figures correspond with those in an analysis by Glenn,<sup>7</sup> according to which 7 per cent of a series of patients had complications at the time of the initial symptoms and approximately 40 per cent had had symptoms for less than one year. It is thus apparent that acute cholecystitis may develop either early or late during the course of gallstones.

Although there is no general agreement concerning the pathogenesis of acute pancreatitis, a significant and fairly constant finding is its association with gallstones.<sup>8</sup> Calculi have been reported in 70 to 81 per cent of cases of acute pancreatitis,<sup>9</sup> which is therefore usually considered a complication of gallstones. In the present series 10 patients (4 per cent) had acute pancreatitis (Table 4). These cases,

TABLE 4. Duration of Symptoms in Patients with Acute Pancreatitis.

DURATION	No of Cases	PERCENTAGE
Less than 1 yr.	5	50.0
1-2	3	30.0
10 or more	2	20.0
Total	10	

according to Abell's<sup>10</sup> classification, included acute pancreatic edema, acute pancreatic necrosis and acute pancreatic necrosis with hemorrhage. Five patients in this group had symptoms for less than one year before operation, 2 having acute pancreatitis with their first attack of biliary distress; 3 had symptoms for two years and 2 for thirteen and seventeen years, respectively. The average duration was 3.9 years. Acute pancreatitis was often an early complication than a late sequela of gallstones. Thirty-two patients (12 per cent) had stones in the common duct (Table 5). The average duration

TABLE 5. Duration of Symptoms in Patients with Cholecholelithiasis.

DURATION	No of Cases	PERCENTAGE
Less than 1 yr.	10	31.2
1-2	4	12.5
3-9	1	3.1
10 or more	5	15.6
Total	32	

of symptoms was 5.6 years, which with the exception of the cases of carcinoma of the gall bladder was the longest for those with complications. The duration period varied from less than one year to twenty years, except for 1 case with symptoms for forty years. Ten patients (31 per cent) were operated on before the end of twelve months, in fact, 3 were found to have stones in the common duct at operation following the first attack of colic. Fifty

average duration of symptoms was 4.9 years, which is practically the same interval as in the cases without complications. Although 35 per cent of the patients were operated on after having had symp-

seven per cent, however, had had symptoms for three or more years. The incidence of stones in the common duct relative to the duration of symptoms seems to be a subject of disagreement among authors. Heyd<sup>11</sup> reports the frequency of such stones as ranging from 1.9 per cent of patients with symptoms for less than two years to 16 per cent of those with symptoms from ten to thirty-five years, whereas Lahey and Swinton<sup>12</sup> report that 46 per cent of patients with common-duct stones have had symptoms for less than one year.

It is generally accepted that gallstones predispose to malignant change in the biliary tract.<sup>13,14</sup> They are found in most cases of carcinoma of the gall bladder,<sup>15</sup> and considerable evidence has been presented that stones precede biliary carcinoma.<sup>16</sup> On the other hand, the usual incidence of carcinoma of the gall bladder in cholelithiasis is only 0.5 to 1.5 per cent,<sup>17</sup> although it has been pointed out that its frequency is probably low because many patients undergo early cholecystectomy.<sup>11,13,14</sup> Of 3 patients (1 per cent) in the present series with carcinoma of the gall bladder, 2 also had choledocholithiasis. Symptoms had been present for six, twenty-seven and forty years respectively, — an average of twenty-four years. Although carcinoma has been reported when symptoms were of short duration,<sup>18</sup> most reports state that they were present for ten or more years.<sup>13,16,19</sup> Its rarity as a complication of gallstones<sup>14</sup> discounts it as a real risk in the temporary postponement of cholecystectomy.

In cases of long-standing gallstones, scarring, thickening and deformity of the liver edge are considered by some investigators as evidence of localized hepatitis,<sup>20</sup> whereas others think that the gross appearance of the liver is of little prognostic value.<sup>21</sup> Livers that look damaged, it is stated, frequently show no appreciable evidence of parenchymal change. The liver has been shown to have a tremendous reserve power,<sup>22</sup> and many hepatic functions are maintained even when only 20 per cent of the total liver tissue is normal.<sup>23</sup> Risk of operation because of liver damage can usually be combated and minimized by adequate preoperative management, and the optimum time of operation can be determined by appropriate liver-function tests.

Whether gallstones are a factor in diabetes or whether there is a metabolic process common to both is unsettled. Gallstones do appear to develop more frequently in patients with diabetes than in the general population at large,<sup>14</sup> and complications of gall bladder seem to be more frequent in diabetic than in nondiabetic.<sup>24</sup> Six patients in the present series had diabetes in addition to gallstones. The complication of diabetes in addition to gallstones, however, cannot be proved. The time of onset of symptoms before operation and the time of onset of symptoms after cholecystectomy in the gall bladder has not been determined. Accordingly, the time factor for the development of biliary complications must resolve itself as appears.

At the George F. Baker Clinic in Boston, it has been found that diabetic patients require as much insulin after cholecystectomy as before.<sup>24</sup>

### CONCLUSIONS

It is evident from this study that the sequelae of cholelithiasis do not appear at any well-defined time interval after the presence of stones is first determined. Biliary complications may be present with the initial attack or appear shortly after calculi are first demonstrated. On the other hand, complications may not develop for many years after cholelithiasis has been diagnosed or may never occur in spite of recurring attacks of biliary colic over many years. Yet in general it can be accepted that the longer symptoms continue in cholelithiasis, the greater is the possibility of biliary complications. The likelihood of the development of complications in any person known to harbor gallstones must be constantly borne in mind.

Biliary calculi should be removed, if practicable, as soon as possible after their presence is known. Today, however, because of wartime exigencies and the shortage of medical and hospital personnel, any elective operation such as cholecystectomy for gallstones without complications may have to be deferred. Until operation can be arranged, every effort should be made to reduce the dangers inherent in delay. Patients who cannot be operated on promptly should be put on a strict regimen of diet and hygiene in an effort to lengthen the period between attacks. They should be warned of the dangers of biliary complications and the necessity of seeking prompt medical advice. Should patients develop acute biliary emergencies, — and perforation of the gall bladder may occur within twenty-four hours of the onset of acute cholecystitis, — hospital beds should be promptly available, even if it means that hospitals postpone the admission of patients scheduled for elective operations. If these safeguards are observed, it should be possible for the duration of the war to minimize the risks involved in the postponement of operation for gallstones.

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early surgery. It is equally the responsibility of the medical profession to bend every effort toward the provision of prompt hospital facilities. Acute cases should not be refused admission even if such admission requires the taking over of ward beds and the release of beds earmarked for elective treatment. In this age, when so much progress is being made in medicine and surgery, every effort should be made by surgeons in the furtherance and encouragement of such a program despite the economic situation as it exists. The economic plea for delay means complications involving not only a greater mortality rate but also greater morbidity and economic loss. Dr. John Fallon, Worcester: No paper could be more timely than this. When lifeboats are crowded and we have the law of the sea. Now hospitals are crowded and we have another law: "The sickest first." The elevator-hour patient, if compellingly sick, must come before him who has borne the aggravations of the waiting list. Otherwise hospitals are only hotels and we are hazarding a life to keep a promise. One of the operations we can usually delay is cholecystectomy. But when and for how long? Cholecystitis without stone can be delayed to the end of the war or, so far as I am concerned, the end of the next war. On the other hand, jaundice or a suspicion of peritoneal inflammation demands hospitalization. Between these two extremes where do we stand? The man with attack increasing in strength, frequency or length is lucky. He has a stone lodged in the pelvis or cystic duct, and empyema, perforation or progress into the common duct are in the offing. Still, he is lucky because he has been warned. He can beat the storm. The others, those with colics every rainy Tuesday, can wait a little. The law of averages is with them, although Dr. Bearse shows that a considerable minority have serious complications within a year of diagnosis, and I remember at least two deaths in the first attack. In other words, the law of averages says we can wait a little, but we have no data concerning how long "a little" is. If we cannot say how long to delay, we can say how much harm delay does. Of a group of 1000 Fallon Clinic patients whose chief lesion was nonmalignant disease of the gall bladder or ducts, I did. Note that we are considering not the risk of operation but the risk of the disease. The series, to be fair, includes the 76 patients whom we tried to tide over without operation or until a more hopeful time for operation. Seven of these 76 deaths may be called accidents. These were the overwhelming attacks coming, without reasonable warning, in the old and decrepit and the emboli and coronary occlusions. Fifteen deaths were the fault of a doctor, — oftenest myself, — shock, pneumonia (which is decreasing since the use of spinal anesthesia) or plain bad surgery done by someone before us or by one of us. But the majority, 19, were due to delay, despite adequate warning, until there were these deaths might have been saved by better judgment or better technique. True, but if there had been no delay, miracles would not have been needed. And the argument is academic when the mortality of operation for uncomplicated disease is a small fraction of 1 per cent.

Fundamentally, delay killed these 19 patients just as it contributed toward the deaths of several others and, among living and dead, added up a sum of misery not reducible to figures.

How long can we delay? Certainly long enough to give priority to the acute patient but not to a patient with a hernia that can be controlled by truss. Who knows where the fuse is set on a time bomb? If that bomb is buried under your own liver, delay takes courage. I should have to wait longer nowadays, but when I found out several years ago that I had gallstones, I delayed just one day, and only because the day was Christmas. When I tell my patients that story they say, "Ah, but you went to a good surgeon."

Dr. I. S. Otis, Meriden, Connecticut: The pathologic state of the gall bladder cannot always be safely estimated by any physical or laboratory test, hence the danger of delay. Not infrequently the problem arises of persuading a patient to have surgery when he or she seems to have recovered. Such patients are counting certain trouble, and the necessity for operation should be insisted on at the first evidence of suggested symptoms. Here the attending physician is invaluable in leading the patient to such a decision.

According to Ellason and Stevens, there is liable to be serious biliary damage because of the long period of the disease existing before the acute attack precipitating the operation. Often pancreatitis and hepatitis, together with cardiac and renal disease, result in operative and postoperative deaths. It is odd that although surgeons are almost universally agreed that acute appendicitis should be treated surgically as an emergency, — within hours, not days, — in acute cholecystitis, in which it is generally agreed that one cannot foretell the severity of the pathologic condition, they sometimes wait an indefinite time before instituting surgery. This position seems doubly untenable when some writers report perforations as having occurred within twenty-four hours. However, in an analysis of 35,000 cases, shows that 20 per cent progressed to perforation, with a mortality of 10 per cent. Others give frequencies of perforation up to 45 per cent. MacDonald in 1941 pointed out that gall-bladder disease in its early stages is often viewed with "alarming nonchalance". It is this very attitude that may be responsible for the frequently disappointing results following belated operation. Graham illustrates the danger of procrastination by citing the mortality rates for cholecystectomy. After two attacks it is 2 to 3 per cent, after three or more attacks 8 to 9 per cent, in the presence of jaundice 10 to 12 per cent, and with pancreatitis 50 per cent.

In Dr. Bearse's series, it is to be noted that 103 patients (40 per cent) had one or more complications at operation, with an average duration only two years greater than that in the cases without complications. Add to this fact that 35 per cent had symptoms for less than one year and 47 per cent for less than three years, and one sees that the principle of decreasing the best surgical judgment should remain firm. Despite the pleas of patients concerning the lack of domestic help to care for children, as well as the desire of workers to remain constantly on their jobs, they should not be permitted to alter the surgeons' primary desire to reduce mortality and morbidity. The latter should continue to advise

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## LOW-BACK PAIN AS THE PRESENTING SYMPTOM OF MALIGNANT BREAST TUMORS

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**P**RIIMARY malignant tumors of the female breast that have metastasized to the vertebral column and bony pelvis are not infrequently overlooked. These patients are at times erroneously treated for the numerous other causes of backache, such as "lumbago," "sciatica," sacroiliac strain and retroversion of the uterus. The frequency of diffuse skeletal metastases from relatively small malignant nodules in the breast is a well-recognized clinical fact, but the subject has not been extensively discussed or become crystallized in the literature.

Lamarque<sup>1</sup> in his discussion of skeletal metastases from breast cancer makes the point that many of his patients complained of vague bone pains or suffered from pathologic fracture before a small tumor, until then unrecognized, was discovered in the breast. Ducuing<sup>2</sup> maintains that the invasion of the skeleton may present the first symptoms of a breast cancer, which are frequently ignored. This can be manifested by a bony tumor, pains in the bones or spontaneous fracture. The initial cancer may pass unnoticed either because of its small size or because of large breasts that mask the tumor, the breast tumor then revealing itself late. Warren and Witham<sup>3</sup> state that the first symptoms noted in malignant tumors of the breast are at times due to metastases, such as pathologic fracture or evidence of intracranial pressure. The prime purpose of this paper is not only to reiterate and emphasize that spinal metastases from an unrecognized breast tumor may be the cause of chronic low-back pain and may cause the presenting symptoms, but also to discuss the significance of such metastatic patterns in the light of new knowledge.

### CASE REPORTS

**CASE 1.** A 52-year-old woman complained of low-back pain of 3 months' duration. She had been treated for a sacroiliac strain and myofibrositis of the lumbar muscles, with diathermy and local heat.

Physical examination revealed a well-nourished, middle-aged woman with negative physical findings except for a nodule in the middle of the right border of the right breast. The breasts were somewhat large and pendulous. A lymph node in the axilla was palpable. Biopsy revealed a scirrhous carcinoma of the breast. X-ray examination of the spine showed involvement of the 4th and 5th lumbar vertebrae and some infiltration in the body of the ilium.

The diagnosis was carcinoma of the breast with metastases to the spine.

**CASE 2.** A 50-year-old woman had been treated for low-back pain with diathermy and local heat for 1 month prior to her present illness. She was wearing a sacroiliac belt. A nodule the size of a walnut was found above the nipple in the right breast. Biopsy proved this to be a scirrhous carcinoma, and roentgenologic study of the spine revealed the lesions of bony metastases involving the sacroiliac joint and the lower lumbar vertebrae.

**CASE 3.** A 31-year-old woman underwent a ventral uterine suspension for low-back pain 3 years prior to her present illness. One year after the operation a nodule was found in the left breast; it was pronounced clinically non-malignant and a diagnosis of cystic mastitis was made. She became pregnant and delivered a normal child. Three months post partum, while bending down to pick up her baby she felt a sudden "crack" in the back and could not stand up.

A physician made a diagnosis of sacroiliac strain and strapped the back. The condition grew steadily worse, and the pain developed a left sciatic distribution. X-ray examination of the spine was negative. The patient was treated with short-wave therapy, strapping and a sacroiliac belt, obtaining only transient relief. Two months later, it was found that there was some degree of anesthesia over the left anal fold, as well as loss of the left Achilles reflex. A tentative diagnosis of cauda-equina tumor or herniation of a nucleus pulposus was made. Lipiodol studies of the spine were negative.

Throughout this period no attention was paid to the breast. The pain became severer and a back brace was ordered, with little relief. Subsequent examination revealed the breast mass to be the size of a hen's egg; it was hard and adherent to the skin. An enlarged node was found in the axilla. A diagnosis of carcinoma of the breast with bone metastases was made. Re-examination by x-ray, 4 months after the original films were taken, showed generalized spinal and pelvic metastases and some metastatic nodules in the skull.

The patient eventually died, and autopsy proved the lesion to be an adenocarcinoma of the breast with generalized spinal and skull metastases. The original x-ray films were reviewed but no demonstrable lesions were observed.

**CASE 4.** A 55-year-old woman complained of pain in the back of 5 months' duration. She had been treated for sacroiliac disease and low-back pain.

Physical examination showed tenderness over the left sacroiliac joint and pain in the left sciatic notch, with radiation down the left leg and over the right hip joint. A mass the size of a large hazel nut, adherent to the skin and non-tender, was palpated in the right upper quadrant of the right breast. A few lymph nodes were palpated in the right axilla.

The diagnosis was carcinoma of the breast with spinal and pelvic metastases. This was confirmed by punch biopsy. X-ray study of the spine and pelvis showed metastatic involvement of the lumbar vertebrae, left sacroiliac joint, left ischium and right hip.

### DISCUSSION

It may seem elementary to suggest examination of the breasts in women suffering from back pain, but the 4 cases presented illustrate the importance of this procedure in all patients with complaints referable to the skeletal system. Such examination should be routine even if the patient is completely unaware of any mammary nodule or ulceration. As illustrated by Case 3, bone lesions may not become apparent roentgenologically until considerable bone tissue has been destroyed. Negative x-ray findings in the presence of bone pain and a nodule in the breast should not rule out bone metastases, at least early in the disease, and the patient should be followed by subsequent bone x-ray studies. Case 3 also illustrates the time-consuming, uncomfortable and extensive procedures that are often performed

before the true nature of the primary disease is recognized. This patient had lipiodol studies of the spinal canal, orthopodic appliances had been prescribed, and she had even been accused of hysteria.

\* \* \*

Batson's<sup>4</sup> has described the probable route of metastases from the breast. According to this concept there is a vast intercommunicating system of veins between the epidural and vertebral veins and the veins of the thoracicacoabdominal cavity. This system of veins has no valves and the venous pressure is extremely low. With every increase of intra-abdominal and intrathoracic pressure, the intratruncal pressure is raised to sufficient heights to permit the blood to flow into this vertebral system of veins. Thus there is a reversal of blood flow that bypasses the cardiopulmonary circuit. Since this system has no valves, a flow of blood occurs up and down the spine and into the skull. It does not involve the heart and lungs, and has many connections with the thoracicacoabdominal system of veins. According to Batson, this provides a ready vehicle for the explanation of aberrant metastatic patterns and removes the stumbling block of the absence of lung involvement. The course through a patent foramen ovale, he states, is no longer necessary to explain this lung paradox. This system of vertebral veins is also called the meningogastrochondroid system. By means of injections of radio-opaque dyes and subsequent roentgenography, as well as postmortem intravenous injection of the mammary veins, Batson has demonstrated the role of these veins in spinal metastases from malignant tumors of the breast. He has shown that this vast vertebral plexus is constantly the site of a physiologic reversal of blood flow and communicates with the veins of the spinal column as well as those of the breast. Thus the spine may be the site of metastases from breast tumors long before the original lesion has been recognized. Batson writes:

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Four cases of carcinoma of the breast are presented in which pain from metastatic foci to the spine and bony pelvis was the first evidence of neoplastic disease. Negative bone x-ray films early in the disease, in the presence of bone pain and a mass in the breast that has proved malignant, should not rule out bone metastases. X-ray studies should follow. The probable route of metastasis by way of the vertebral veins, as described and suggested by Batson, is discussed. Metastatic foci to the lower back and pelvis from a primary breast tumor should be considered as a not uncommon cause of low-back pain. Breasts of all patients, especially women, should be examined routinely for tumors, particularly in the presence of low-back or pelvic pain.

## SUMMARY

These patients demonstrate clinically Batson's contention that metastases to the spine do occur directly via the vertebral veins. Interestingly, all except Case 3 showed involvement of the lower spine and pelvis. Case 3 showed the diffuse type of bone metastasis. One might expect the other three patients to show more involvement of the shoulder girdle and upper spine, as Batson demonstrated with his injection experiments of the breast. One can explain this, however, on the basis of the flow in the valveless veins descending the spine. It might be noted in passing that since the vertebral veins richly anastomose with the thoracicacoabdominal regions, other malignant neoplasms, such as pelvic and lung tumors, may also metastasize early to the spine. These may also show the picture of bone pain as the presenting symptom.

## MEDICAL PROGRESS

### INSECT VECTORS OF DISEASE (Continued)

VLADO A. GETTING, M.D., DR.P.H.\*

#### CONENOSE BUGS

The conenose bugs belong to the order Hemiptera, family Reduviidae.<sup>91</sup> They are commonly called "assassin bugs," "kissing bugs," "corsairs," "black corsairs," "wheel bugs" and "bedbug hunters." Predatory in nature, several species protect themselves by biting, whereas others have developed a distinct habit of sucking mammalian blood. Two genera, *Triatoma* and *Rhodnius*, contain conenose bugs of medical interest. Although a few species are worldwide in distribution, the majority are found in the Western Hemisphere, particularly in the high cold regions of the Andes.

Most conenose bugs are active runners and good fliers. Since white man's invasion of South America, these bugs have become domesticated and now can be found in the straw huts of Indians in Brazil. They live in the cracks of the more permanent structures, and live on man and domestic animals. Adults of both sexes bite; the larvae and nymphs are wingless and therefore restrict their activity to the house. Nocturnal in habit, they quickly run for shelter when suddenly exposed to light. The bite is usually painless,<sup>92</sup> so that a person bitten in his sleep is not awakened. The blood meal, lasting from a few minutes to half an hour, is followed by defecation of liquid feces. All the conenose bugs that bite man or animal infected with *Trypanosoma cruzi* become infected and retain the infection until death.<sup>93</sup> Although adult trypanosomes occur sparingly in the blood of patients with Chagas disease, nevertheless, when taken up by conenose-bug nymphs or adults, they lose their flagella and are transformed into "leishmania forms." In this stage, the trypanosomes multiply rapidly and develop into "crithidia," which in turn develop in the hindgut of the bug into the infective trypanosome forms. These infective forms then enter a new host (man or other vertebrate) through the medium of the infected feces deposited on the mucous membrane of the mouth or nose or on the conjunctiva of the eye or through the puncture wound created by the bug bite, an abrasion or an excoriation of the skin. Brumpt<sup>94</sup> proposed a method of diagnosis that calls for an insect vector (xenos) being fed on a suspected case, the bug being examined eight days later for the developmental stages of the trypanosomes.

*Tryp. cruzi* occurs naturally in armadillos, opossums, squirrels, certain monkeys, bats, cats, dogs and a California wood rat. *Triatoma gerstakeri*

naturally infected with *Tryp. cruzi* were studied by Packchianian<sup>95, 96</sup> in southern Texas. Naturally infected triatoma have also been found in Arizona by Wood<sup>97</sup> and in California and Texas by Davis.<sup>98</sup> The nymphs of *Tr. gerstakeri* often occur in the nests of wood rats. *Tr. megista* is the most important vector of Chagas disease in the greater part of Brazil, and *Rhodnius prolixus*, primarily a human parasite, is the chief vector in northern South America.

The conenose bug is also incriminated as a mechanical vector of Western equine encephalomyelitis and of yellow fever.

The destruction of reduviid bugs is difficult as fumigation or insecticide spraying in tropical huts is impractical. Mosquito nets at night and adequate screening of houses offer protection against the adult bugs; however, the small nymphs are difficult to eliminate. Burning of infected huts may have to be performed as a last resort.

#### LICE

The order Anoplura, family Pediculidae, includes the sucking lice that subsist on blood. They attack man and other vertebrates and are vectors of typhus fever,<sup>99</sup> trench fever<sup>65</sup> European relapsing fever and, less frequently, plague. Urticaria and melanoderma (Vagabond's disease) may follow from the bite. Because of irritation produced by the bite, scratching may result in cutaneous pyogenic lesions. The head louse may transmit typhus fever, and is also accused of transmitting favus and impetigo. So far as is known, the pubic or crab louse is not a vector. The body louse is by far the most important vector. Man and his clothing are the chief disseminators of body lice. Whenever the temperature of the environment approaches that of the body, the louse leaves the vicinity of the body and wanders about in search of other hosts. Hence, under crowded conditions, where several human beings are huddled either in search of heat or shelter from enemy action, the louse is afforded ample opportunity for new infestations. Typically, lousiness and louse-borne diseases are cold-weather affairs. A temperature of 86 to 90°F.—that which exists between the skin and clothing—is ideal for lice. Eggs are attached to the fibers of clothing, especially woolens. Cotton and silk are less likely to harbor lice, owing to the lack of fiber. The eggs of the head louse are attached to the hairs covering the head, whereas the nits of the crab louse can be found on the pubic hair or on the hair of the eyebrows and the beard.

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fever and Rift Valley fever. Ticks are also an important cause of anemia in domestic animals, a female tick ingesting a hundred times her weight in blood. Moreover, certain species cause tick paralysis through venom contained in the salivary secretions of the mature female at a particular time of her life before she drops from the host on whom she is feeding.<sup>109</sup> This paralysis is ascending in type and may cause death. In northwestern United States and British Columbia the common wood tick *Dermacentor andersoni* and in Australia *Ixodes holocyclus* have, in several cases, been reported as causing paralysis, respectively, of man and also of animals, calves, sheep and dogs.

The soft ticks are less parasitic than the hard ticks. The nymphs and adults are rapid feeders and tend to remain in the habitat of their hosts. There are two medically important genera, *Argas* and *Ornithodoros*.<sup>110</sup> *Argas persica* (the fowl tick, miteana bug, blue bug or abode tick) is worldwide in distribution and an important poultry parasite whose habits are similar to that of the bedbug. It has a long life-span, — over four years if unfed, — and is a vector of fowl spirochetosis. Of the Ornithodoros ticks, there are some thirty species feeding on birds, mammals and reptiles,<sup>111</sup> and one species has experimentally transmitted rickettsial infections. Living in nests and burrows or the homes of man, they feed rapidly and intermittently. Their bite is painful, leaving an itching wheal. Of the six known species in the United States, *Ornithodoros coriaceus*, known as *pavlovii* in the southwestern states and *deckeri*, is most venomous and feeds on cattle and deer. *O. talaje* is found in Minnesota, Wisconsin, New York, the southwestern states and Central America; it is a vector of relapsing fever and lives in the dust, cracks and crevices of walls of rest-houses and huts. It feeds on birds and mammals including man.

The hard ticks are shorter lived than the soft ticks. Their eggs are usually deposited on the ground; the larvae climb grass stalks to await small rodents and other suitable hosts. Nymphs and adults similarly await larger hosts, including man. *Dermacentor andersoni*, the western wood tick, is the most important vector of Rocky Mountain spotted fever and tularemia and also is capable of transmitting equine encephalomyelitis. A three-host tick, the larva and nymph feed on small rodents, such as field mice and squirrels, the adults on larger animals, such as horses, cattle, sheep, wolves and rabbits. Alan is an accidental host. *D. variabilis*, the common dog tick, is frequent in the eastern United States as far north as Cape Cod; it is a vector of tularemia and Rocky Mountain spotted fever,<sup>112</sup> and it has been used experimentally to transmit of Ixodidae have been experimentally proved to be capable of transmitting these diseases. *Hama-physalis leporis palustris*, a widely distributed rabbit

The order Siphonaptera contains the wingless, hard-bodied, small, brown, parasitic fleas, which are provided with powerful legs adapted for jumping.<sup>65</sup> Adults of both sexes bite and suck blood; they are active and may jump upward 20 cm. or horizontally for almost twice that distance. Fleas leave the body of a dead host as soon as it begins to cool, seeking a new host. Often showing a preference for certain parts of the body, the adults are normally body parasites. The nests or dens, however, of animal and birds are normal breeding places. Fleas feed at frequent intervals, usually at least once a day, but occasionally much oftener since they are easily disturbed while feeding and seldom complete a meal. Even with a filled digestive tract, a flea may pass unaltered blood in the feces and still be feeding.

Fleas are important vectors of plague<sup>104</sup> and endemic typhus fever and mechanically transmit yellow fever. The ordinary rat flea *Xenopsylla cheopis*, after feeding on an infected animal, may have its digestive tract full or even possibly blocked by solid growths of plague bacillus. Such fleas may regurgitate blood containing the plague bacillus into the wound, or may pass the organism into the feces, which in turn may be introduced into the skin either through the puncture or as a result of an abrasion. Probably the smallest known flea is the jigger, sand flea or chigoe<sup>102</sup> (the chigger is not a flea but a larval mite<sup>103</sup>). This flea is an especially annoying pest in the tropics and subtropics, where it may occur in extremely large numbers, especially in burrows into the skin, particularly beneath the toes, under toenails and in tender parts of the feet to lay eggs, and receives nourishment from the blood. The abdomen of the female flea begins to swell to the size of a pea, the posterior end barely reaches beyond the swelling of the host's skin and forms a plug for the hole. The eggs mature and are expelled through the tip of the abdomen, the female then shrivels up and drops out or is expelled by ulceration. Treatment of this flea is difficult and consists of aseptically removing the entire flea and consequent disinfection.

## TICKS

Ticks are not true insects and belong to the class Arachnida, order Acarina.<sup>104</sup> The family Argasidae is comprised of soft ticks, while the family Ixodidae consists of hard ticks. Of the order Acarina, ticks are the most important transmitters of disease. They are now known to be vectors of relapsing fever (*Borrelia duttoni* type), Rocky Mountain spotted fever,<sup>105</sup> *fièvre boutonneuse*, African tick fever, Sao Paulo fever, tularemia, Chagas disease, louping ill, Western equine encephalomyelitis,<sup>106</sup> and American Q fever,<sup>107, 108</sup> and they occasionally transmit yellow

tick, transmits naturally both Rocky Mountain spotted fever and tularemia.<sup>114</sup>

All tick vectors transmit disease from adult to eggs, to larvae and hence to nymphs and adults of the next generation. This hereditary transmission of disease complicates the control of tick-borne diseases. Soft ticks are controlled by methods used against bedbugs. Hard ticks, especially *D. andersoni* and *D. variabilis*, are extremely difficult to control. Tick-proof clothing, examination of oneself and one's clothing after passing through tick-infested areas, avoidance of underbrush and of herding sheep through an infested field, picking off ticks with tweezers and burning over underbrush, with the elimination of small rodents, are some control measures that have proved of value. Immunization against Rocky Mountain spotted fever in persons who are likely to be exposed is available by a vaccine prepared by the United States Public Health Service.<sup>115</sup>

A tick infected with Rocky Mountain spotted fever is not infectious until some time after attachment to the new host. The rickettsias are reactivated after a period of one and three-fourths hours to two or more days. Similarly, tick bites early in the spring are not likely to result in infection whereas tick bites in the fall are much more dangerous.

#### TRANSMISSION OF DISEASE BY INSECT VECTOR

##### *Infection of Vector*

The vector of a disease is primarily infected by biting a person or animal that is a blood carrier of the disease in question, whereby the insect ingests the blood containing the infecting organisms. In certain of the insect-borne diseases, such as Rocky Mountain spotted fever,<sup>116</sup> the infective agent is transmitted by the primary insect host through the egg stage to succeeding generations. Occasionally the infective agent is passed from one insect to another during copulation. One or more of these methods may prevail in the case of certain diseases. Usually, when the infective agent is passed from one generation to another in the vector, the disease is persistent or long lived. The infective agent is not fatal to the vector, and there is evidence that this interrelation of the infective agent and the primary insect-host is sufficient to propagate the disease without the intervention of another host. This apparent symbiosis or survival of the infective agent in the insect host, with its transmission to subsequent generations, indicates that the disease is an old or usual one of that insect and that the infection of man is accidental, the latter being a true secondary host and unnecessary for the continued existence of the disease. These conditions are illustrated by the tick *D. andersoni* and the rickettsias of Rocky Mountain spotted fever.<sup>117</sup>

##### *Infection of Host*

The infective agent is transmitted usually to man or some other animal as a result of biting or attempted biting by the infected insect host. In some diseases the infected insect injects the organisms into the tissues of man in the act of biting; this is true in malaria; when the mosquito injects saliva into the tissue to maintain the blood fluid, malaria plasmodia are introduced into the victim. The regurgitation of stomach contents is occasionally the manner of infecting the bitten person; it is in this manner that fleas spread the bacteria of plague. In other instances, the surface of the skin is contaminated by the feces or glandular secretions of the infected insect, or by the infective material of an insect that is crushed on the skin as it bites. This infective material reaches the blood of the bitten person by being inoculated into the bite wound or through abrasions made by scratching or rubbing the bitten area. The infective agents of some of the insect-borne diseases, notably the bacteria of plague and the spirochetes of relapsing fever, can pass directly through the unbroken skin.

##### *Biologic Transmission*

Some of the organisms that cause insect-borne disease in men must undergo a stage of development in the body of the insect host before they can be transmitted to the human host. In such a disease both the insect host and man are necessary for the survival of the disease, and the absence of either results in the control or disappearance of the disease from the affected area. Control of this type of insect-borne disease is more feasible than that of the type in which the infective agent is passed through eggs from one generation of the insect host to the next.

Malaria and filariasis are examples of diseases that undergo this type of biologic development. The time required for the development of the parasite in the insect host constitutes the extrinsic period of incubation. The length of this extrinsic incubation varies for different organisms but is fairly constant for each organism, although influenced by temperature changes; colder weather lengthens the extrinsic period of incubation.

The life cycle of certain of the infective agents that undergo biological development includes a sexual and an asexual phase. The host in which the sexual phase occurs is called the "definitive host," whereas the one in which the asexual phase is passed is known as the "intermediate host." The insect vector or the human host may serve as a definitive or an intermediate host. In malaria, the sexual phase of the plasmodium occurs in the mosquito, which is the definitive host, and man is the intermediate host.<sup>118</sup> In filariasis, on the other hand, of which the infective agent is *Wuchereria bancrofti*,

It is evident that most of the important diseases of man with which epidemiologists are concerned fall into the group of diseases with biologic transmission. Those that undergo cyclopropagative and propagative transmission are of chief concern, since in these diseases the parasite undergoes multiplication and hence the survival of the parasite in the arthropod host is more certain and the infection of man is statistically likelier.

It is necessary to appreciate these facts in planning an attack on a disease suspected of being insect transmitted, for only in this way can the attack on the disease be logically and properly directed.

#### PREVALENCE OF INSECT-BORNE DISEASES

Within certain limits, the geographic distribution of an arthropod-borne disease is governed by the distribution and prevalence of the insect host. Consequently, an insect-borne disease can prevail only in districts where the insect hosts are indigenous and where environmental conditions are favorable for their continued existence. For example, yellow fever, which is spread by the *Aedes aegypti* mosquito, is a disease of the tropics, where that mosquito is indigenous. In the days of clipper ships, however, yellow fever outbreaks occurred in Boston. They usually started in the middle of summer and always disappeared with the first frost. The disease began near the wharves and spread in the direction of prevailing winds. Apparently what took place was that *A. aegypti* mosquitoes were brought north from the tropics by the clipper ships and then bred in the open barrels of water that were conveniently placed on the wharves as protection against fire. The mosquito continued to survive so long as environmental conditions were favorable, and the disease spread throughout the summer, but with the first frost the mosquito was killed and the outbreak subsided. Subsequent outbreaks were due to reimportation of infected mosquitoes.

Because the tropics and subtropics supply favorable conditions for mosquitoes, mosquito-borne diseases are prevalent in these regions. Conversely, louse-borne diseases occur most frequently in cold and temperate regions, since the conditions produced by cold, namely, the wearing of heavy clothing, crowding in houses for heat and inadequate personal hygiene, favor the propagation and dissemination of lice. This has been well illustrated by the occurrence of typhus fever in the concentration camps in Poland and in the armies on the Russian front.

Since no insect or arthropod is worldwide in distribution, no insect-borne disease is worldwide in distribution. Moreover, even if the insect vector is present, the insect-borne disease spread by that vector need not be prevalent. A classic example of this is the absence of yellow fever in Asia. For an insect-borne disease to prevail, the following conditions must exist: the vector must be indigenous or be able

man is the definitive host, and the mosquito the intermediate host.

An essential consideration in respect to biologic transmission is the appreciation that in some instances the infective agent undergoes a cyclic morphologic change in the body of the arthropod, whereas in others the parasite undergoes simple multiplication; in still others there is both a cyclic change and a multiplication. It is worth while to examine the different arthropods regarding these two characteristics. Epidemiologists are greatly concerned with these two factors because they affect so much the behavior and the geographic distribution of the disease concerned.<sup>19</sup> Both the interpretation of the observed epidemiologic phenomena and the institution of the indicated control measures are related to these characteristics.

The most complicated mechanism involved in biologic transmission of the infective agent is known as the cyclopropagative cycle. In this, the parasite undergoes a developmental cycle, with morphologic changes, and at the same time multiplies in the body of the insect host; both are entirely apart from any developmental process or multiplication taking place in man. The classic example of this cyclopropagative development is malaria. The sexual cycle, with multiplication, takes place in the mosquito, the definitive host<sup>20</sup>; and in man, the intermediate host, the plasmodium undergoes an asexual cycle. There are thus an extrinsic incubation period, during which the parasite undergoes change and increases in number in the mosquito, and an intrinsic incubation period, during which the asexual cycle takes place in man.

A second and less complete form of biologic transmission is the cyclodevelopmental cycle, in which the micro-organisms undergo a cyclic change in the arthropod host but do not multiply there. Here, the best example is filariasis, in which the worms undergo morphologic changes in the mosquito but do not increase in number. This disease, filariasis, was the first to be proved to be insect-borne, when Patrick Manson made his fundamental discovery in 1878.

The third type of biologic transmission is termed the propagative cycle, since the etiologic agent undergoes simple multiplication without morphologic changes. A typical example of this type of transmission is that of the rickettsias of typhus fever in lice.

#### Mechanical Transmission

When it is not necessary for the infective agent to undergo a period of development or multiplication in the arthropod host, biting vectors may transmit the disease mechanically. Usually, the infective agent spread by this means of transmission is a bacterium. The spread of bubonic plague or of typhoid fever is a good example of mechanical transmission.

TABLE 1. *Vectors of Arthropod-Borne Diseases modified from "Insects as Vectors of Virus Diseases," by James S. Simmons in Virus and Rickettsial Diseases (Cambridge: Harvard University Press, 1940).*

DISEASE	CLASS: ORDER:	ARACHNIDA				INSECTA				DIPTERA			
		ACARINA	PARASITOID	ANOPLURA	HEMIPTERA	SIPHONAPTERA	MOSQUITOES	SAND FLIES	GNATS	BUFFALO GNATS	GADFLIES	STABLE FLIES	TSETSE FLIES
		TICKS	HARVEST MITES	SUCKING LICE	BEDBUGS	CONENOSE BUGS	FLIES						
<i>Helminths:</i>													
Filaria		—	—	—	—	—	—	—	—	—	—	—	—
Onchocerciasis		—	—	—	—	—	—	—	—	—	—	—	—
<i>Protozoa:</i>													
Malaria		—	—	—	—	—	—	—	—	—	—	—	—
Texas cattle fever		—	—	—	—	—	—	—	—	—	—	—	—
African sleeping sickness		—	—	—	—	—	—	—	—	—	—	—	—
Chagas's disease		—	—	—	—	—	—	—	—	—	—	—	—
Leishmaniasis		—	—	—	—	—	—	—	—	—	—	—	—
Espundia		—	—	—	—	—	—	—	—	—	—	—	—
<i>Bacteria:</i>													
Enteric fevers		—	—	—	—	—	—	—	—	—	—	—	—
Plague		—	—	—	—	—	—	—	—	—	—	—	—
Tularemia		—	—	—	—	—	—	—	—	—	—	—	—
Yaws		—	—	—	—	—	—	—	—	—	—	—	—
<i>Rickettsias:</i>													
Oroya fever		—	—	—	—	—	—	—	—	—	—	—	—
<i>Spirochetes:</i>													
Relapsing fever ( <i>B. duttoni</i> type)		—	—	—	—	—	—	—	—	—	—	—	—
Relapsing fever ( <i>B. recurrentis</i> type)		—	—	—	—	—	—	—	—	—	—	—	—
<i>Rickettsias:</i>													
Typhus fever (epidemic)		—	—	—	—	—	—	—	—	—	—	—	—
Typhus fever (endemic)		—	—	—	—	—	—	—	—	—	—	—	—
Trench fever		—	—	—	—	—	—	—	—	—	—	—	—
Rocky Mountain spotted fever		—	—	—	—	—	—	—	—	—	—	—	—
<i>Flaviviruses:</i>													
African tick typhus		—	—	—	—	—	—	—	—	—	—	—	—
Sao Paulo fever		—	—	—	—	—	—	—	—	—	—	—	—
Tutuagumushi fever		—	—	—	—	—	—	—	—	—	—	—	—
<i>Viruses:</i>													
Yellow fever		—	—	—	—	—	—	—	—	—	—	—	—
Dengue		—	—	—	—	—	—	—	—	—	—	—	—
Pappataci fever		—	—	—	—	—	—	—	—	—	—	—	—
Rift Valley fever		—	—	—	—	—	—	—	—	—	—	—	—
Looping ill		—	—	—	—	—	—	—	—	—	—	—	—
Equine encephalomyelitis		—	—	—	—	—	—	—	—	—	—	—	—
Epidemic encephalitis (Type B)		—	—	—	—	—	—	—	—	—	—	—	—
Epidemic encephalitis (St. Louis)		—	—	—	—	—	—	—	—	—	—	—	—
Poliomyelitis		—	—	—	—	—	—	—	—	—	—	—	—

— = usual method of transmission.  
m = mechanical transmission.  
s = survival of organisms.

Of the rickettsial diseases, epidemic typhus fever is spread by lice and the endemic form by either lice, fleas or mites. French fever is also carried by lice. Rocky Mountain spotted fever,<sup>128</sup> *fièvre boutonneuse*, African tick typhus and Sao Paulo fever are transmitted by ticks, and *Tsutsugamushi* disease or scrub typhus is spread by harvest mites. Of the insect-borne virus diseases, yellow fever, dengue,<sup>129</sup> equine encephalomyelitis<sup>130</sup> and possibly Japanese encephalitis<sup>131</sup> are transmitted by mosquitoes. Louping ill and equine encephalomyelitis are transmitted by ticks,<sup>132, 133</sup> but the latter is known to have been transmitted by the consensu or assassin bugs.

### (To be concluded)

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to become indigenous; the vector must propagate under favorable environmental conditions; the vector must be present in sufficient numbers to spread and maintain an indigenous level of the disease (if the number of vectors is reduced to below this critical level, the disease cannot survive in epidemic proportions); susceptibles must be present and exposed to the vector; an infected person must be bitten by the vector, which must have access to the human host; environmental conditions must permit the vector to bite the infected host and then the to-be-infected host; and, finally, the vector must survive long enough to permit the parasite to undergo the extrinsic incubation period and then bite a new susceptible host. If any one of these conditions is unfavorable, the disease ceases to be epidemic and the cycle is broken, and if the cycle is broken often or long enough, the disease tends to disappear gradually from the area. If, on the other hand, one of the factors that was missing is replaced, the disease can be reintroduced or may assume epidemic proportions in an area where it was formerly endemic.

When the cycle of transmission includes an animal host of the parasite, the prevalence of the disease concerned is modified or entirely governed by the accessibility of the animal host. It is important to note that the survival of the disease and any plan to control it must take into consideration this additional factor. It is this type of disease, namely, animal-arthropod-man, that presents some of the most complicated and fascinating problems of epidemiology.

### CLASSIFICATION OF INSECT-BORNE DISEASE

Arthropods transmit not only diseases of man and other animals<sup>121</sup> but also diseases of insects and plants,<sup>122</sup> such as the diseases of the cabbage butterfly<sup>123</sup> and the various mosaic diseases of tobacco and tomatoes. So far as man is concerned, seven types of etiologic agents are transmitted by arthropods (Table I). These are as follows: helminths (round worms), protozoa; bacteria; bartonellas, spirochetes; rickettsias; and viruses.

The helminths are transmitted only by Diptera — filariasis by mosquitoes, gnats and gadflies<sup>124</sup> and onchocerciasis by Buffalo gnats.

Among the protozoal diseases are malaria, spread by mosquitoes and the most devastating insect-borne disease in the world, Texas cattle fever, spread by ticks, African sleeping sickness, spread by tsetse flies, and Chagas' disease, spread by ticks and assassin bugs.

The most important insect-borne bacterial diseases are plague,<sup>125, 126</sup> spread by fleas, and tularemia, spread by ticks and gadflies.

Oroya fever, caused by a bartonella, is transmitted by sand flies.

The spirochetes of relapsing fever<sup>127</sup> are transmitted by ticks.

TABLE 1. *Vectors of Arthropod-Borne Diseases modified from "Insects as Vectors of Virus Diseases," by James S. Simmons in Virus and Rickettsial Diseases (Cambridge: Harvard University Press, 1940).*

DISEASE	CLASS: ORDER:	INSECTA										STABLE FLIES	TSETSE FLIES	FILTH FLIES
		ARACHNIDA			HEMIPTERA			DIPTERA						
		TICKS	ACARINA	PARASITOID MITES	ANOPLOURA	SUCKING LICE	BEDBUGS	CONENOSE BUGS	SIPHON- APTERA	MOSQUITOES	SAND FLIES	GNATS	BUFFALO GNATS	GADFLIES
<i>Helminths:</i>														
Filaria		—	—	—	—	—	—	—	—	x	—	x	—	—
Onchocerciasis		—	—	—	—	—	—	—	—	—	—	—	x	—
<i>Protozoa:</i>														
Malaria		x	—	—	—	—	—	—	—	x	—	—	—	—
Texas cattle fever		—	—	—	—	—	—	—	—	—	—	—	—	—
African sleeping sickness		—	—	—	—	—	—	—	—	—	—	—	—	—
Chagas's disease		x	—	—	—	—	s	x	—	—	—	—	—	x
Leishmaniasis		—	—	—	—	—	—	—	—	s	?	—	—	—
Espundia		—	—	—	—	—	s	—	—	—	?	—	—	—
<i>Bacteria:</i>														
Enteric fevers		—	—	—	—	—	—	—	—	—	—	—	—	—
Plague		—	—	—	—	—	s	—	x	—	—	—	—	—
Tularemia		x	—	—	—	—	—	—	—	sm	—	—	—	—
Yaws		—	—	—	—	—	—	—	—	—	—	—	x	—
<i>Rickettsias:</i>														
Oroya fever		—	—	—	—	—	—	—	—	—	x	—	—	—
<i>Spirochetes:</i>														
Relapsing fever ( <i>B. duttoni</i> type)		x	—	—	—	—	—	—	—	—	—	—	—	—
Relapsing fever ( <i>B. recurrentis</i> type)		—	—	—	—	—	?	—	—	—	—	—	—	—
<i>Rickettsias:</i>														
Typhus fever (epidemic)		—	—	—	—	—	—	—	—	—	—	—	—	—
Typhus fever (endemic)		—	—	—	x	—	—	—	x	—	—	—	—	—
Trench fever		—	—	—	—	—	—	—	—	—	—	—	—	—
Rocky Mountain spotted fever		x	—	—	x	—	—	—	—	—	—	—	—	—
Fever douglouze		—	—	—	—	—	—	—	—	—	—	—	—	—
African tick typhus		x	—	—	—	—	—	—	—	—	—	—	—	—
Sao Paulo fever		x	—	—	—	—	—	—	—	—	—	—	—	—
Toutugamushi fever		x	—	—	—	—	—	—	—	—	—	—	—	—
<i>Viruses:</i>														
Yellow fever		m	—	—	—	—	m	m	m	x	—	—	—	—
Dengue		—	—	—	—	—	—	—	—	—	—	—	—	—
Pappataci fever		—	—	—	—	—	—	—	—	x	—	—	—	—
Rift Valley fever?		—	—	—	—	—	—	—	—	—	x	—	—	—
Louping ill		s	—	—	—	—	—	—	—	s	—	—	—	—
Equine encephalomyelitis		x	—	—	—	—	—	—	—	—	—	—	—	—
Epidemic encephalitis		—	—	—	—	—	—	—	—	—	—	—	—	—
Epidemic encephalitis (Type B)		x	—	—	—	—	x	x	—	—	—	—	—	—
Epidemic encephalitis (St. Louis)?		—	—	—	—	—	—	—	—	—	—	—	—	—
Poliomyelitis?		—	—	—	—	—	—	—	—	—	—	—	—	—

x — usual method of transmission.  
m — mechanical transmission.  
s — survival of organisms.

intestinal symptoms. Peristalsis was referred to as high-pitched and hyperactive which is suggestive of obstruction, but without a more elaborate description it does not really establish the diagnosis. Obstruction is often associated with tinkling, hollow, peristaltic sounds whose occurrence is synchronous with crampy pain.

The patient had normal-colored feces, and no guaiac test is recorded. The white-cell count was normal, which suggests that infection or necrosis

I have recently seen a patient who had a sigmoidoscopy, and we have already noted the lack of evidence of inflammatory reaction or bowel necrosis, the presence of which would lead one to conclude that, if she had an intussusception, it was not affecting the blood supply of the bowel.

So the problem becomes one of trying to discover why this patient had an intussusception at the age of sixty and, secondarily, why this intussusception did not do her any more harm than it did.

I have recently seen a patient who had a sig-



FIGURE 1. Roentgenogram after Barium Enema Showing Tumor Mass Advanced into Transverse Colon Pulling the Cecum after It.

of the bowel was not a part of the picture. "This impression is borne out by other vital signs.

Now we come to the x-ray films, and I am sure that they will either make or break the diagnosis. Unfortunately no roentgenologist is present, so we shall have to rely on our own interpretation of the films.

There is a sausage-shaped mass in the right-hand portion of the transverse colon, which apparently advances at times over toward the splenic flexure. When it is in that position, the cecum is shortened and the terminal ileum is no longer visible. I do not see how one can avoid the diagnosis of intussusception in the presence of such findings. Only one of the many spot films, however, shows the characteristic dimple in the advancing end of the in-

Another question to be answered is, What was the leading point of the intussusception? I have already mentioned that the x-ray films show a sausage-shaped mass without the characteristic dimple in the leading portion. This suggests that this portion is not the bowel wall itself but a fairly large mucosal or intramural tumor. If this were the case, it would

under discussion. Another question to be answered is, What was the leading point of the intussusception? I have already mentioned that the x-ray films show a sausage-shaped mass without the characteristic dimple in the leading portion. This suggests that this portion is not the bowel wall itself but a fairly large mucosal or intramural tumor. If this were the case, it would

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor\**

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### CASE 31121

#### PRESENTATION OF CASE

A sixty-year-old married woman was admitted to the hospital complaining of abdominal pain, nausea and vomiting.

Seven years before admission, three months after repair of a cystocele, the patient first noticed a localized burning sensation in the back and pain under both costal margins, with morning nausea, vomiting and occasional diarrhea. This pain came in episodes that were intermittent until five years before admission, when the pain became persistent. A Graham test one year later revealed failure of filling and the presence of a gallstone in the gall-bladder area. Three years before admission she had an acute attack of pain in the right upper quadrant, with nausea and vomiting. Since that time she had had frequent morning headaches and mild upper abdominal pain, which were relieved by vomiting. During the previous two years she had also had mild lower abdominal pains that were relieved by episodes of diarrhea. About a month before admission a barium enema in the Out Patient Department showed a transient delay in filling at the hepatic flexure, and a smooth, round, filling defect was seen projecting into the lumen of the transverse colon (Fig. 1). Barium later passed around this defect to the cecum and it was possible to outline a smooth ovoid mass, measuring about 9 by 5 cm. On palpation or contraction of the bowel the mass moved distally, and on a post-evacuation film it reached

the midtransverse colon. With this movement of the mass the ascending colon became shortened. These findings were confirmed by a second barium enema.

Physical examination revealed an obese, well-developed woman. Examination of the heart and lungs was negative. The abdomen was moderately tender in the suprapubic area; there was no spasm. The liver and spleen were not felt, and no masses were palpated. Peristalsis was high pitched and hyperactive. A pelvic examination was not remarkable. A rectal examination revealed brown feces.

The temperature, pulse and respirations were normal. The blood pressure was 190 systolic, 120 diastolic.

The serum nonprotein nitrogen, protein and chloride were normal. Examination of the urine was negative. The white-cell count was 4100, and the hemoglobin 80 per cent. An oral Graham test was positive.

On the sixth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. FRANCIS D. MOORE: At the age of fifty-three this patient began to have gastrointestinal symptoms that were compatible with, although not typical of, gall-bladder disease. One year later a gallstone was shown to be present, and this was undoubtedly regarded as the cause of her symptoms. At the age of fifty-eight, two years before she came to the hospital, a new set of symptoms arose, which evidently had to do with the other end of the gastrointestinal tract, since the pain was in the lower abdomen and associated with diarrhea. It is true that she had had some diarrhea with her supposed gall-bladder attacks, but it apparently was not prominent. The new symptoms, however, were often relieved by the diarrhea, a train of events that strongly suggests an intermittently obstructing lesion.

Physical examination does not give us many clues but it does mention that the patient was obese and well developed, findings that one would not expect if she had had any sort of malignant tumor for either the two-year period or the seven-year period, accompanied respectively by the upper and lower gastro-

\*On leave of absence.



On cholecystectomy and again after the operation. In both the ascending and transverse colon. When it was in the transverse colon, the cecum was elevated as though the advancing tumor had pulled the cecum after it—an intussusception, with the tumor itself leading. This, as Dr. Moore has stated, accounts for the fact that the usual dimple in the intussusceptum was not seen. This dimple is more frequently seen in children, for then a tumor is seldom present, the leading part being the bowel itself; in adults, an absence of the dimple is almost the rule. That the tumor was soft and compressible is shown on the film of the contracted bowel, the tumor being much longer and narrower than the stated measurements. The appendix lay in the right upper quadrant below the liver, where it presumably had been drawn upward with the cecum when the tumor was advanced by peristalsis.

### CASE 31122

#### PRESENTATION OF CASE

*First admission.* A sixty-four-year-old Polish freight handler was admitted to the hospital with

jaundice.

The patient was in good health until three weeks

prior to admission, when he suddenly became

nauseated and vomited some whitish material. The

feeling of nausea lasted several hours, after which

he felt better. A few days later the nausea recurred,

accompanied by a "heavy feeling" in the epig-

astrum but no pain. He vomited several times,

and his appetite became poor. Two weeks before

entry, he noticed that his skin was becoming yellow.

At the same time his stools became light colored and

his urine dark. He stopped work and rested but

did not improve. The heavy feeling in his epig-

astrum persisted as the jaundice increased, and

he had two more attacks of vomiting. There was

no itching, chills, fever or change in bowel habit.

He lost about 8 pounds over a period of two weeks.

During this same period he noted slight ankle

edema, disappearing overnight.

The patient had had an attack of "double pneu-

monia" fifteen years prior to admission, following

which he continued to have a chronic cough, which

was worse in the morning and evening and pro-

ductive of about 30 cc. of white sputum each day.

He had never noted blood streaking or chest pain.

About twelve years before entry, following severe

trauma to the genitalia, the right scrotal sac had

remained enlarged, without alteration in

size.

Physical examination on admission revealed a

well-developed and well-nourished, deeply icteric

man in no distress. The fingers were clubbed. There

was bilateral marked arcus senilis, and the fundi showed moderate arteriosclerotic nicking. The chest resonance to percussion and diminished breath sounds and fremitus. Diffuse dry squeaks and rhonchi were heard, with sticky rales at the bases posteriorly. The heart sounds were distant. The liver was palpable three fingerbreadths below the costal margin, and the edge was smooth, sharp and nontender. The gall bladder could not be felt. The right scrotum contained a firm, 6-cm., nontender mass that failed to transmit light. A portion of the testis could be felt attached to the mass posteriorly. The temperature was 99°F., the pulse 70, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

Examination of the blood revealed a red-cell count of 3,650,000, with 12 gm. of hemoglobin, and a white-cell count of 8000, with 78 per cent neutrophils. The smear revealed a hypochromic microcytic anemia with many target cells. The urine had a specific gravity of 1.020, with a ++ test for albumin and a ++ test for bile and with a positive test for urobilinogen in a dilution of 1:2. The sediment contained 10 to 15 white cells and an occasional coarsely granular cast per high-power field. The stools were clay-colored, soft and occasionaly guaiac positive. The serum protein was 5.7 gm. per 100 cc. with an albumin-globulin ratio of 1:3. The van den Bergh was 15.2 mg. per 100 cc. direct and 26.2 mg. indirect. The prothrombin time was normal, and the cephalin flocculation test negative. A bromsulphalein test showed 100 per cent retention. A galactose tolerance test, employing the injection of 50 cc. of a 50 per cent solution of galactose intravenously, revealed a blood level of 12.4 mg. per 100 cc. after 60 minutes, and one of 8.1 mg. after 75 minutes. The serum nonprotein nitrogen was normal, and the chloride was 95 milliequiv. per liter. Agglutination tests with the patient's serum against *Proteus vulgaris* X19, XK and X2 and *Leptospira icterohaemorrhagiae* and *L. canicola* were negative. The Hinton test was negative.

A roentgenogram of the chest showed no evidence of active disease in the lungs. The right costophrenic sinus was obliterated, owing to old adhesions. The heart showed no definite enlargement. A gastrointestinal series was negative. Duodenal drainage was productive of 20 cc. of whitish, translucent fluid in an hour. Half an hour after the injection of 40 cc. of a saturated solution of magnesium sulfate, another 20 cc. of similar fluid was obtained. A smear of the sediment revealed no sodium bilirubinate or cholesterol crystals, nor were any bile-stained leukocytes seen. Culture revealed abundant colonies of colon bacilli.

The patient was placed on a high-carbohydrate, high-protein, high-vitamin, low-fat diet and given bile salts (0.1 gm. Degaolol, three times a day). An

account for the lack of x-ray dimple and it might also suggest that, although the leading point was in the midtransverse colon, the actual amount of intussuscepted bowel was only a matter of a few centimeters above the ileocecal valve. The latter would make us feel more comfortable about the lack of evidence of bowel necrosis.

Such a smooth tumor could be a lipoma, fibroma, neurofibroma or lymphoma of the bowel wall. It would have to be in the terminal ileum or right at the ileocecal valve, because there is no evidence that the colon itself was being intussuscepted without pre-existing ileocecal intussusception.

Of these tumors, lymphoma is probably the most frequent, but lymphoma in the gastrointestinal tract tends to be multiple; even though occasional cases are recorded in which resection was curative, such cases are the exception. Furthermore, if this were lymphoma, I should expect that the patient would have had some bleeding from the region of the tumor itself.

I am therefore going to select a lipoma as the likeliest leading point for this intussusception. My diagnosis is intramural lipoma of the terminal ileum, with chronic ileocecal intussusception.

Possibly I am overlooking something in not trying to relate this lesion to the patient's antecedent gall-bladder disease. Although it is true that a gall-stone might have ulcerated through into the colon, I can see no reason why it should not have passed down to the rectum; furthermore, one would not expect that its attempted passage down the bowel would have produced retraction and shortening of the cecum. This latter chain of events, it seems to me, can be produced by intussusception or attempted passage of a long pedunculated submucosal tumor and by nothing else.

#### CLINICAL DIAGNOSES

Polypoid tumor of the right colon, with intussusception.  
Cholelithiasis.

#### DR. MOORE'S DIAGNOSES

Submucosal pedunculated lipoma of the terminal ileum, with ileocecal intussusception.  
Cholelithiasis.

#### ANATOMICAL DIAGNOSIS

Submucosal lipoma of ascending colon.

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At operation Dr. Allen carefully palpated the entire right colon and was unable to demonstrate the polyp that he had hoped to find. The bowel, however, had not been too well prepared. The bowel was not opened, and no resection was performed. There were dense inflammatory adhesions in the region of the gall bladder and the duodenum, and the hepatic flexure was

slightly adherent to this region. A shriveled, chronically inflamed gall bladder, within which was a 1.5-cm. stone, was removed. The common duct was not explored.

The patient left the hospital on the seventh post-operative day. Most of her symptoms were relieved for several months, but she still had occasional crampy abdominal pain to the right of the umbilicus.



FIGURE 2.

Another barium enema still disclosed the polypoid lesion in the colon, and it was decided to operate again.

Once more Dr. Allen was unable to palpate a tumor in the ascending and transverse portions of the colon. Using a needle, air was carefully aspirated from the large bowel and the needle hole was then closed. When the right colon was mobilized, an extremely soft tumor could be felt in the ascending colon. About 18 cm. of the terminal ileum and the right colon was resected, and an ileotransverse colostomy was performed.

The tumor proved to be, as Dr. Moore predicted, a submucosal lipoma measuring 9 by 6 by 4 cm.; it was attached by a mucosal stalk 3.5 cm. in diameter at a point 10 cm. distal to the ileocecal valve (Fig. 2). The tumor was soft, malleable and easily compressible, which accounts for the great difficulty the surgeons had in palpating it through the serosal surface.

Will you comment on the x-ray films, Dr. Schulz?

DR. MILFORD D. SCHULZ: This patient was examined on several occasions — twice prior to the

that we have seen positive Hinton tests in the presence of liver damage. I say that because two or three years ago I became interested in the subject and have a collection of 5 cases in which this was so, with no other evidence of syphilis to go with it.

We have excluded the first and second groups under the retention type of jaundice. I do not believe that it was a Hanot's type of cirrhosis because the appearance of the liver would have told us whether or not it was a hypertrophic biliary type. At the first exploration we are told that there was no obstruction. Yet I cannot escape the final conclusion that there was obstruction, that they found some sort of process that obstructed the biliary system and that a great deal of liver-cell necrosis was also present.

If I have to make a choice in the correct order I hardly know what to say. I believe that he had malignant disease, and my first choice is carcinoma. Where are we going to put it? He might have had metastases in the liver and in the spine causing peripheral nerve changes; it might have been primary in the testicle injured years before, or it might have been a primary tumor of the colon with metastases to the liver and somewhere along the common duct that caused obstruction. That is my first choice. My second choice is that he had that rare thing causing a positive guaiac test in the stools, a carcinoma localized in the duodenum around the ampulla of Vater. It could still be carcinoma of the pancreas, part of it involving the ampulla of Vater and head of the pancreas, and I am still supported in this by the positive guaiac test, and that is why I may reverse the order and put it down as my first choice. My third choice is a regurgitation-type necrosis of the liver, a severe form of the toxic group.

DR. CASTLEMAN: Your first choice is carcinoma involving the head of the pancreas?

DR. CHAPMAN: Yes, and the ampulla of Vater.

DR. CASTLEMAN: How do you explain the normal common duct at operation?

DR. CHAPMAN: One other thing I meant to bring out was the matter of the common-duct drainage. The first time it is described the sediment revealed no sodium bilirubinate, cholesterol crystals or bile-stained leukocytes. I think it was Bockus' who found that most patients with silent stone in the common duct show evidence by drainage of either bilirubin crystals or bile-stained crystals. In the last drainage, no bile was seen but there were a few bile casts and bilirubin crystals. Possibly, a silent stone jammed down toward the ampulla should be my fourth choice.

DR. CASTLEMAN: You still have to assume that the common bile duct was distended.

DR. CHAPMAN: But the patient did not have complete obstruction. Obviously he had intermittent

blood bilirubin. The first is the anoxic group — pernicious anemia, transfusion reaction, hemolytic jaundice, paroxysmal hemoglobinemia, phenylhydrazine poisoning and other types of blood disease that produce hemolysis. The second group comprises febrile diseases, and the attending physicians thought of this because they looked for positive agglutination tests with *Leptospira icterohemorrhagiae*, *L. canicola* and various strains of *Proteus vulgaris*. The third group is Hanot's cirrhosis of unknown cause.

Then we come to the regurgitation type. Here, the plasma gives a direct van den Bergh reaction because it contains bile that has backed up secondary to obstruction of the biliary tract, possibly with injury to the bile canaliculi. This may be due to three causes — necrosis of the liver cells, frank obstruction in the biliary system and catarrhal jaundice, cause undetermined. The necrosis of liver cells from toxic agents may cause jaundice of either kind or of both types together.

The patient was a Polish freight handler, and although he may have been a heavy drinker, there is no history of alcoholism, so we have no cause to think of alcoholic hepatitis with liver-cell necrosis. Now let us go back and look at the laboratory evidence and fit it into this classification. The laboratory tests do not favor the retention type as well as the regurgitation type. In favor of the retention type are the target-cell anemia, the urobilinogen, the negative duodenal drainage and the high indirect van den Bergh. In favor of regurgitation jaundice are the bile in the urine in considerable amounts, the high phosphatase, which goes with liver damage and especially necrosis of liver cells, and the final duodenal drainage before operation, because the record clearly describes cholesterol crystals and bile casts but no bile. Obviously these laboratory data do not give us the answer.

What are the clinical facts, divorced from the laboratory data, that help us arrive at a diagnosis? He was a sixty-three-year-old man who had had a tumor of the testis, who was jaundiced and who had a big spleen and liver. He undoubtedly had necrosis of the liver cells, because we know that he improved after exploration. Then came pain over the liver, more jaundice, weight loss and the appearance of general weakening and certain reflex changes in the leg. He developed a positive Hinton test, and above all he had guaiac-positive stools. I am so glad to get complete data on that because it is an important observation and outweighs all the laboratory evidence that was presented. This man had blood in his stools. Where was that blood coming from? From the gastrointestinal tract? Or is it possible for the necrosis of the liver cells in the regurgitation type to be severe enough to cause a positive guaiac test in the stools? As for the positive Hinton test, I am going to dismiss syphilis. I know

exploratory laparotomy was performed on the ninth hospital day. The liver presented an unusual granular mottling and seemed edematous, suggesting some form of hepatitis rather than cirrhosis. The gall bladder was normal, readily compressible and no stones were present. The head of the pancreas was soft. The common bile duct was of normal size and appearance. No biopsy specimen was taken.

Following the operation the patient seemed to improve. The van den Bergh gradually fell to 5.8 mg. direct and 8.8 mg. indirect, the stools became light brown, but no urobilinogen was present in the urine. He was discharged on the forty-third hospital day, to be followed in the Out Patient Department.

*Second admission* (ten weeks later). Following discharge, the patient continued to improve for about a month. The jaundice became less noticeable but never disappeared, and he gained a few pounds. About six weeks prior to admission he began to feel weak, with attacks of pain in the right upper quadrant and epigastrium, which were often stabbing in character, and occasional nausea. His stools again became light colored. He developed some unsteadiness of gait. At about that time, the van den Bergh was 15.8 mg. direct, and the serum protein 6.31 gm. per 100 cc., with an albumin-globulin ratio of 0.83. The cephalin flocculation test was negative, and the urine contained no urobilinogen.

On readmission the patient appeared cachectic and still deeply icteric. The liver was four finger-breadths below the costal margin and slightly tender. There was evidence of a small amount of fluid in the abdomen, and minimal pitting edema of the ankles was present. The deep tendon reflexes were hypoactive in the upper and absent in the lower extremities. There was a questionable extensor plantar response on the left.

A roentgenogram of the chest revealed no definite change from the previous examination. A gastrointestinal series showed considerable curling of the esophagus but no definite varices. The liver was enlarged, and the spleen slightly enlarged. The stomach was slightly compressed by the liver and spleen and showed rather marked thickening of the mucosal folds.

The serum protein was 5.76 gm. per 100 cc., with an albumin-globulin ratio of 0.73. The van den Bergh was 12.4 mg. direct and 13.6 mg. indirect. The cephalin flocculation test on one occasion was  $\pm$  after twenty-four and  $++$  after forty-eight hours, and on another occasion negative. The alkaline phosphatase was 34.8 units per 100 cc. The prothrombin time, serum nonprotein nitrogen and chloride were normal. The cholesterol ranged from 147 to 250 mg. per 100 cc. The blood Hinton and Wassermann tests were positive. Urine examination revealed a  $++++$  test for bile and numerous tyrosine crystals. Urine urobilinogen varied from

negative to positive in a dilution of 1:16. Duodenal drainage revealed a few bile casts and bilirubin crystals but no bile. The stools were light brown and occasionally guaiac positive.

On the thirty-first hospital day a laparotomy was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. EARLE M. CHAPMAN: "The stools were clay colored, soft and occasionally guaiac positive." I should like to know how many stools were guaiac positive.

DR. BENJAMIN CASTLEMAN: The first stool examination was guaiac negative; the second, positive; the third,  $++$ ; the fourth,  $+$ ; and the fifth, negative.

DR. CHAPMAN: That is an important contribution.

It is interesting that this man had disease in the chest. The x-ray does not reveal it. Physical examination says that rales were present, and I think that rales are a sign of disease. This case I believe is the epitome of the diagnostic problem, because one is presented with laboratory evidence which at one and the same time indicates an obstructive process and a nonobstructive type of jaundice. Obviously the attending physicians were puzzled as to which it was, for the first time they made a great effort to prove that it was obstructive and later on that it was nonobstructive. On the first admission, they must have been convinced that it was obstructive because the evidence leans more on that side and the patient was explored. But still the surgeon failed to give them a diagnosis. I want to pause and say that a biopsy of the liver at the first exploration would have been helpful.

The next thing I want to point out is that the head of the pancreas was described as soft. It has always been my opinion that the head of the pancreas is hard and firm and that at operation the surgeon sometimes has difficulty distinguishing the normal head of the pancreas from carcinoma.

Following exploration the patient improved. That is revealing and throws the diagnosis over into the nonobstructive field. I am sure that was the thought when he left the hospital. He finally returned and seemed to go back into the obstructive category, because he was again explored.

In going through the steps of making a diagnosis, it is helpful to use Rich's<sup>1</sup> classification of jaundice. He distinguishes two major types, retention jaundice and regurgitation jaundice, the latter being the obstructive and the former the nonobstructive, based on the fundamental pathology of the process. In retention jaundice the bilirubin is increased in the plasma, and since all of it is not removed by the liver cells an indirect van den Bergh reaction results. With this increase in blood bilirubin the kidneys excrete an increased amount of urobilin. What causes this? Three groups of disorders increase

involve the hepatic ducts, the extrahepatic ducts, the cystic duct and the ampulla of the gall bladder. DR. CASTLEMAN: The patient died following the operation, and at autopsy we found a tumor involving both hepatic ducts. It had apparently begun in one of the hepatic ducts and had extended out into the hilus for a few centimeters so that Dr. Wallace could feel it, but it had also involved the cystic duct. Beyond the tumor there was 6 cm. of perfectly normal uninvolved common bile duct. The tumor, which proved to be an adenocarcinoma, had spread through the lymphatics to involve the surface of the body and tail of the pancreas, but the head of the pancreas was perfectly normal. This patient also had bronchiectasis and a cyst in the tail of the pancreas. There was no evidence

Peritoneoscopy showed severe bile stasis, biliary cirrhosis and marked dilatation of the bile ducts. We found a bile duct measuring 2 or 3 mm. in diameter in the biopsy specimen, which must have been taken from the periphery of the liver, so that this patient really had a hydrophepatosis. There was definite bile-duct proliferation (Fig. 1). Following this procedure, Dr. Wallace operated. He might tell us what he found. DR. RICHARD H. WALLACE: I explored this patient on both occasions. I was much interested the first time because two days before I had operated on a woman with painless jaundice and removed a common-duct stone. This is especially noteworthy because of the relative infrequency of painless jaundice with common-duct stone. In the series

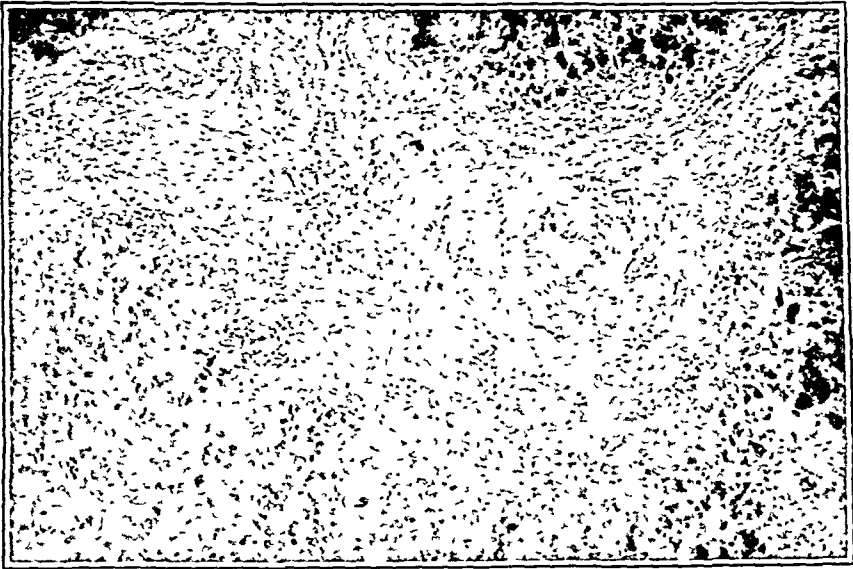


FIGURE 1. Photomicrograph of Liver.

of the diffuse cystic disease of the pancreas that is occasionally seen in children and that may be associated with bronchiectasis. In both lower lobes the bronchi were distended to the very periphery of the lobes and contained large quantities of viscid yellowish-green material.

DR. WALLACE: This man, who had an obstructive jaundice, had no chills or fever either at the first admission or at the second, nor did he give a history of any in between times. I wonder if that would have been helpful if that had been brought out.

DR. JONES: I do not know. It is surprising that he did not have elevation of the temperature, because in patients with metastatic or primary involvement of the liver with new growth, fever is frequently an essential part of the picture. DR. CHAPMAN: As a teacher of physical diagnosis I should like to emphasize, and I am sorry that Dr. Merrill Sosman is not here, that here we have still

that Dr. Allen and I reviewed less than 2 per cent of the patients with common-duct stones were without pain. At the first exploration, I found a normal gall bladder, a normal common duct and a normal pancreas, and except for the abnormal liver findings, the exploration was entirely negative. Following the biopsy of the liver by Dr. Benedict it was brought out that possibly there was a common-duct stone without a dilated common duct, which I had never seen. We rather hoped that we might find this at the second exploration. At that time, the gall bladder was still collapsed and on aspiration perfectly clear white mucoid material was obtained. The common duct was normal, the liver was smooth, there was a hard nodular mass that was not present at the first exploration. During the six-month interval between explorations it had grown down to

obstruction because he was well after the first operation. Manipulation and pressure may have forced drainage around it.

DR. WILLIAM W. BECKMAN: I was impressed at the time of admission, before the laboratory work was done, by the fact that he stated that one day he was completely well and the next day he was sick and started to vomit. After a week he noticed jaundice. This seemed to me to be in favor of hepatitis of some sort. The laboratory data did not seem to support that diagnosis. Finally, an exploration was performed and I was delighted that my original idea was supported. I thought that he certainly had hepatitis but could not understand why he did not get better after two months. He was readmitted and there was a great deal of controversy, but we finally decided to re-explore.

DR. JACOB LERMAN: There are always differences of opinion about some clinical points. I saw this man in the Out Patient Department. A routine follow-up note said that he was better. I was quite sure that he was not, because the jaundice was just as severe, although the color of the skin had changed. It turned brown rather than green. I thought that his jaundice was complete and persistent and had not changed much since his stay in the hospital. The stools were noted as occasionally clay colored but usually brown. We checked that by doing bile determination on the brown stools and found that they did not contain any bile. Consequently the chances are that they were always equivalent to clay-colored stools.

DR. CHAPMAN: How did you know they were brown?

DR. LERMAN: They looked brown to the examiner and to the patient.

DR. CHESTER M. JONES: I saw the patient toward the end of his stay on the first admission and later on in the second admission. My feeling was much like that of Dr. Beckman, — that he had an acute episode of damage to the liver which might well have been on an infectious basis, — and I thought he ought to be treated for liver failure rather than anything else.

I remember seeing the first specimen of duodenal contents, and there is little reason to believe that the interpretation of the sediment was incorrect. There was no evidence of bile pigment, bile casts or crystals. In other words, no bile was obtained. I do not know about the second drainage. When I first saw this man I thought the picture was that of infection and I did say that there might be an intrahepatic block due to the type of infection that goes with infection of the common duct — cholangitis. Dr. Wallace's description at the time of the first operation was entirely consistent with a biliary type of obstruction that had not arrived at cirrhosis but presented a smooth, finely granular liver, with mottled discoloration.

The second time I saw him I still thought he had primary intrahepatic disease and that such was going to be found. If the biopsy at that time showed a biliary type of involvement, one had a right to explore the common duct again to see if there was any local tumor or other obstruction, such as a gallstone.

About the positive guaiac in the stool, the presence of occult blood can be found in any type of jaundice, regardless of its nature. It is found commonly if the jaundice is severe and of long standing. I think that it is not of diagnostic significance. In a group of seriously jaundiced patients there was a positive guaiac test in at least 40 or 50 per cent. This finding of occult blood is probably due to the fact that there is a tendency to spontaneous bleeding associated with a lack of prothrombin.

DR. FLETCHER H. COLBY: Did I understand that you seriously considered tumor of the testicle as the primary focus, with metastasis in the liver, as well as somewhere in the common duct and spine to explain the reflex changes? Would it not be unusual to have tumor for twelve years and not to have it metastasize before this? He was operated on and the surgeon found no demonstrable disease in the region of the gall bladder. We had one somewhat similar patient at the Huntington Hospital who, nine years before, had been given heavy external radiation. The only symptom of recurrence that this man had was jaundice. He was operated on with a diagnosis of possible gall-bladder disease, and he had a huge mass pressing on the common duct, a metastasis from the testicular tumor.

DR. JONES: Infiltration of the liver would not cause this picture.

#### CLINICAL DIAGNOSIS

Carcinoma of hepatic ducts.

#### DR. CHAPMAN'S DIAGNOSIS

Malignant disease: (?) carcinoma of head of pancreas, involving ampulla of Vater, (?) carcinoma of colon, with metastases to spine, liver and about common duct, (?) carcinoma, metastatic, to liver and about common duct from testicular tumor.

Common-duct stone?

#### ANATOMICAL DIAGNOSES

Adenocarcinoma of hepatic ducts, with metastases to pancreas.

Cirrhosis of liver, obstructive type, with acute hepatitis.

Bronchiectasis.

Cyst of pancreas.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Wallace operated on this man after a peritoneoscopic biopsy had been done.

Peritoneoscopy showed severe bile stasis, biliary cirrhosis and marked dilatation of the bile ducts. We found a bile duct measuring 2 or 3 mm. in diameter in the biopsy specimen, which must have been taken from the periphery of the liver, so that this patient really had a hydrophepatosis. There was definite bile-duct proliferation (Fig. 1). Following this procedure, Dr. Wallace operated. He might tell us what he found.

DR. RICHARD H. WALLACE: I explored this patient on both occasions. I was much interested the first time because two days before I had operated on a woman with painless jaundice and removed a common-duct stone. This is especially noteworthy because of the relative infrequency of painless jaundice with common-duct stone. In the series

DR. CASTLEMAN: The patient died following the involve the hepatic ducts, the extrahepatic ducts, the cystic duct and the ampulla of the gall bladder. operation, and at autopsy we found a tumor involving both hepatic ducts. It had apparently begun in one of the hepatic ducts and had extended out into the hilus for a few centimeters so that Dr. Wallace could feel it, but it had also involved the cystic duct. Beyond the tumor there was 6 cm. of perfectly normal uninvolved common bile duct. The tumor, which proved to be an adenocarcinoma, had spread through the lymphatics to involve the surface of the body and tail of the pancreas, but the head of the pancreas was perfectly normal.

This patient also had bronchiectasis and a cyst in the tail of the pancreas. There was no evidence

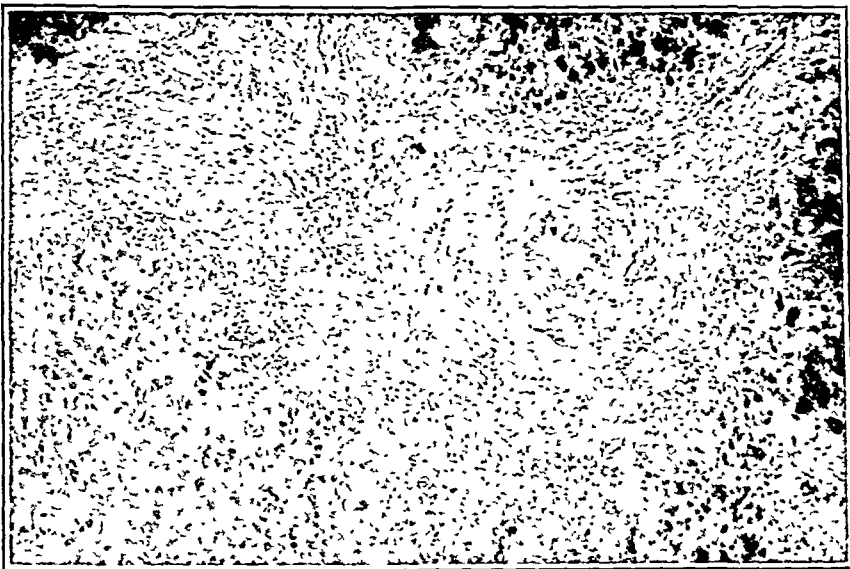


FIGURE 1. Photomicrograph of Liver.

that Dr. Allen and I reviewed less than 2 per cent of the patients with common-duct stones were without pain.

At the first exploration, I found a normal gall bladder, a normal common duct and a normal pancreas, and except for the abnormal liver findings, the exploration was entirely negative. Following the biopsy of the liver by Dr. Benedict it was brought out that possibly there was a common-duct stone without a dilated common duct, which I had never seen. We rather hoped that we might find this at the second exploration. At that time, the gall bladder was still collapsed and on aspiration perfectly clear white mucoid material was obtained. The common duct was normal, the liver was smooth, bile stained and firm, and at the hilus of the liver there was a hard nodular mass that was not present at the first exploration. During the six-month interval between explorations it had grown down to

DR. CHAPMAN: As a teacher of physical diagnosis I should like to emphasize, and I am sorry that Dr. Merrill Sosman is not here, that here we have still

DR. JONES: I do not know. It is surprising that he did not have elevation of the temperature, because in patients with metastatic or primary involvement of the liver with new growth, fever is frequently an essential part of the picture.

DR. WALLACE: This man, who had an obstructive jaundice, had no chills or fever either at the first admission or at the second, nor did he give a history of any in between times. I wonder if that would have been helpful if that had been brought out.

DR. JONES: I do not know. It is surprising that

another case of bronchiectasis, proved by post-mortem examination, in which x-ray films were negative. Dr. Sosman has in his office at the Peter Bent Brigham Hospital a glass case in which a stethoscope is preserved as a museum piece. I think that we should advise Dr. Sosman to break the glass case and take out the stethoscope, as it still continues to be a valuable instrument in clinical medicine.

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early and the needle reinserted elsewhere. When the intramuscular route is used, absorption is prompt and the drug is rapidly eliminated into the urine so that effective concentrations are difficult to maintain for more than two or, at most, three hours. In severe cases of staphylococcal or *Streptococcus viridans* infections it is often necessary to give 20,000 or 25,000 units every two hours. This means the injection of a volume of 4 or 5 cc. each time, since the use of penicillin in greater concentrations than 5000 units per cubic centimeter often produces excessive local irritation. Furthermore, since it is necessary to repeat the injections throughout the day and night, the patient can have no continuous period of rest, and a physician or trained nurse must always be available to give the injections.

One of the major problems in the use of penicillin, therefore, has been concerned with methods that would simplify its administration both for the patient and for the attending physician and nurses. Several methods have been suggested. These have as their purpose either delaying excretion of the drug by the kidneys or prolonging its absorption from the local site. In either event the attempt is made to maintain an effective level for a longer period after injection or with a smaller amount of penicillin.

One of the methods that has been suggested for accomplishing the first of these purposes involves the principle of "excretory blockade." Rammelkamp and Bradley<sup>2</sup> showed that the excretion of penicillin in the urine was depressed by the simultaneous injection of Diodrast. Para-aminohippuric acid is rapidly excreted by the kidneys and, like Diodrast, has been used in tests of renal function. The former has been used by Beyer and his associates<sup>3</sup> to produce the same result that Rammelkamp and Bradley demonstrated with Diodrast. By intravenous injection of this compound together with penicillin it was found possible to attain and to maintain materially higher concentrations of penicillin in the circulating plasma of animals than are practical without the use of excessive amounts of penicillin. Toxicologic studies indicated that the *p*-aminohippuric acid is nontoxic to mice, rabbits and dogs in the amounts necessary to produce this effect. Previous use of this compound in human beings

has been limited to short periods during renal function tests; hence, the effects of continuous use, particularly in patients with severe infections, is not known, but clinical trials are in progress. No matter how the results of these trials turn out so far as indicating the feasibility of the method or the toxicity of the compound, this type of therapy is obviously not desirable or practical. Although it reduces the dosage of penicillin, it does not obviate the need for constant intravenous infusion. Indeed, careful regulation of the rate of injection of the two compounds simultaneously makes the proper use of this method even more difficult and requires even more constant supervision and control than does the injection of penicillin alone.

Another method involves the intramuscular injection of penicillin in a medium from which it is slowly absorbed. After trials with various oils and other substances, Romansky and Rittman,<sup>4</sup> at the Walter Reed Hospital, have found mixtures of beeswax and peanut oil to be the most satisfactory for this purpose. Preparations of penicillin in this mixture were shown to be quite stable and did not deteriorate when kept at refrigerator, room or body temperature for a period of thirty to sixty-two days. In initial experiments in rabbits, it was found possible to maintain satisfactory levels for six to twelve hours with this mixture, whereas with the same amount of penicillin given in saline solution an effective level was maintained for only two hours. In human subjects, single injections of 41,500 and 66,400 Oxford units were given in 2.0 to 2.4 cc. of the beeswax-peanut oil mixture. Measurable levels were maintained in the blood for six to seven hours, and penicillin was excreted into the urine for twenty to thirty-two hours, indicating that some penicillin was retained in the blood throughout that period. In preliminary trials these workers obtained clinical and bacteriologic cures in 11 of 12 patients with acute gonorrhea by a single injection of penicillin in the beeswax-peanut oil mixture, whereas single injections of a similar amount of penicillin in saline solution were only rarely successful.

A third method that has been suggested involves the use of a continuous intramuscular infusion.<sup>5</sup> Such a continuous drip requires a minimum daily volume of 1000 cc., since it is difficult to control

Furthermore, although they may be somewhat helpful, they do not adequately meet the objections raised to the present methods of administration. It is hoped that simpler methods will be evolved to eliminate the necessity for continuous intravenous injection, which requires constant regulation and involves the danger of thromboses and embolism, or for frequent intramuscular injections, with the resulting discomfort and inconveniences.

While all these methods for prolonging the action of penicillin after parenteral administration are being tried out clinically, progress is also being made toward the development of successful methods of oral administration.<sup>11-13</sup> On the basis of reports already available, it seems likely that the ingestion of penicillin in doses larger than those used intramuscularly and in a suitable medium, particularly one that will counteract the acidity of the stomach, will prove feasible.

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## MASSACHUSETTS MEDICAL SOCIETY COMMITTEE ON LEGISLATION

The following copy of Judge Cabot's decision concerning a petition brought by the Trustees of Middlesex University seeking to revise and reverse the decision of the Approving Authority regarding Middlesex University School of Medicine will undoubtedly be of interest to many members of the Society.

WILLIAM E. BROWNE, *Chairman*

the rate of flow with smaller amounts of fluid. The flow may be regulated at 12 to 15 drops per minute or 50 cc. per hour and can be adjusted so that the total daily volume delivers 100,000 units of penicillin or any other desired amount. Apparently, the rate of delivery, and hence of the absorption, of penicillin by this method is even more difficult to regulate than with intravenous injections. It has therefore been suggested that the needle be left in situ and that the flow be interrupted at regular intervals. Even with this modification the method is not particularly desirable since it requires considerable manipulation and many adjustments, as well as resulting in local discomfort. Apparatus that permits the continuous daily injection of as little as 100 cc. of a solution has been devised by Scottish workers<sup>7</sup> who claim that its use demands little attention.

A simple method of delaying absorption from the ordinary intramuscular injection has been suggested by Trumper and Hunter,<sup>8</sup> of the National Naval Medical Center. These workers have made use of local chilling by means of an ice bag placed over the site of the intramuscular injection for a period of one or two hours before and for five to twelve hours after each injection. A harness is applied to keep the ice bag in place, and the ice is changed every three or four hours. With a single injection of 50,000 to 100,000 units given in this manner they have been able to maintain effective blood levels for five or six hours, as compared with two and a half hours when the same amounts are given intramuscularly without cold applications. By the use of this method cures of acute gonorrhea have been obtained quite regularly with a single injection of 50,000 units of penicillin. This method, however, is cumbersome and does not seem feasible for prolonged therapy.

It is possible that the addition of a vasoconstrictor drug to the penicillin given in a medium in which it is absorbed slowly will result in a further delay of absorption. Adrenalin and longer acting vasoconstrictor drugs, together with gelatin, have been shown to prolong the action of penicillin.<sup>9-10</sup> None of the methods thus far proposed, however, have as yet received adequate clinical trial, particularly in severe infections that require the maintenance of significant blood levels over considerable periods.

## COMMONWEALTH OF MASSACHUSETTS

SUFFOLK, SS:

SUPERIOR COURT  
No. 393180

## IN RE THE TRUSTEES OF MIDDLESEX UNIVERSITY

*Findings, Rulings and Order for Decree*

This is a petition brought by the Trustees of Middlesex University under the provisions of General Laws, Chapter 112, Section 2, as amended by Statute 1936, Chapter 247, seeking to "revise and reverse the decision of the Approving Authority" created by that statute. The petitioner is a corporation chartered by statute in 1937 and operates a medical school called the Middlesex University School of Medicine (hereinafter usually referred to as Middlesex). Although no party respondent is named in the petition, an order of notice was issued to Dr. H. Quimby Gallupe, secretary of the Board of Registration in Medicine, and the Approving Authority, appeared by the Attorney General, and the proceeding was conducted as an adversary one against that body with full scope to each to cross examine witnesses, introduce evidence and in general to be heard as would opposing parties in a suit in equity.

In the first place, it is pertinent to examine briefly the statute above referred to so that the nature of the proceeding should be made clear. The act makes it a condition precedent to the right of any person to take the examination to become a licensed physician that he shall have received a degree of doctor of medicine from an "approved" medical school. Paragraph two of the act allows any medical school to request the Approving Authority to make an inspection of it whereupon it becomes the duty of that body to inspect and either approve the school or notify it what steps it must take in order to gain approval. It is to be noted that there is no provision under this paragraph for a final determination of disapproval. The next paragraph of the act gives a school the right to request approval from the Approving Authority, and it then becomes the duty of the latter, after holding a public hearing, to approve or disapprove. It is to be noted that there is no duty imposed upon the Approving Authority either to make an inspection or a decision as to approval unless so requested although, on the other hand, there is no prohibition to its granting approval without a request. Thus, a school may request inspection, in which case it may receive either approval or a direction as to what it must do to gain approval without incurring the risk of a final decision. Only after the school itself requests a final decision does it incur the risk of disapproval. Only after such final decision of disapproval or withholding approval does the school have the right to file a petition in the court to "revise and reverse the decision of the Approving Authority." The statute as finally extended became operative as to persons who entered a medical school on or after January 1, 1941.

Middlesex first requested an inspection in May, 1941. Pursuant to this request the Approving Authority made an inspection on May 28, 1941, and by letter dated August 1, 1941, notified Middlesex that in order to gain approval it would have to take the following steps:

- (1) Its Board of Trustees shall be reorganized so that the management and control of the medical school shall be vested in trustees who are unquestionably qualified to manage, control and administer such an important institution as a medical school.
- (2) The dean shall be one who is recognized as having had experience in the broad field of medical education and who possesses executive and administrative ability.
- (3) The medical school shall have financial resources adequate for providing medical education which meets generally accepted present-day standards.
- (4) There shall be a faculty of which a majority of the members thereof have attained such eminence in their profession that they are so recognized by their fellow workers in their specialties.
- (5) There shall be adequate clinical material available for teaching purposes for all branches of medicine, with special emphasis on medicine, surgery, pediatrics and obstetrics.
- (6) The facilities, both in space and equipment, for research shall be substantially increased.

Early in 1943, Middlesex again requested an inspection, which was made on April 2 and May 25, 1943, and by letters dated June 25 and July 23, 1943, the Approving Authority notified it that it was deficient in the following respects:

- (1) Although the administrative organization and personnel have undergone changes, they are still inadequate for accomplishing the objectives of the institution.
- (2) The medical school has not the financial resources to provide adequate medical education.
- (3) The faculty falls below acceptable standards in numbers and quality.
- (4) There are insufficient clinical facilities for the teaching of the various branches of medicine.
- (5) The facilities in the Library are inadequate in number and selection.

Again on June 20, 1944, the Approving Authority inspected the school pursuant to its request, and by letter dated July 13, 1944, notified it that the following steps were necessary in order to gain approval:

- (1) That the quality and number of the faculty should be improved.
- (2) That the amount of clinical material available for teaching purposes should be increased.
- (3) That the financial resources of the medical school are not sufficient to provide adequate education and that these resources should be greatly increased.
- (4) That the administrative organization and personnel is still inadequate for accomplishing the objectives of the institution.

At some time shortly before July 17, 1944, Middlesex filed, with the Approving Authority, a written request for approval. Thereupon a hearing was set for July 17, 1944, Middlesex was duly notified, and the hearing was held on that date in the Gardner Auditorium in the State House where all persons desiring to be heard were heard. Middlesex was represented by its attorney who presented such persons as he desired to present the case of the school for approval. Other persons gave their views, and although they were not cross examined by the attorney for Middlesex, there is nothing to indicate that he could not have done so had he desired. The hearing was more in the nature of those that are commonly held by the committees of the legislature than of the kind familiar in judicial proceedings. By letter dated July 20, 1944, the Approving Authority notified Middlesex that "the Middlesex University Medical School is not approved by the Approving Authority for the purposes of Section 2 of Chapter 112 of the General Laws as amended." It is this decision that this petition filed in this court on August 16, 1944, seeks to "revise and reverse."

The statute provides that "the court shall hear the case and finally determine whether or not such approval shall be granted or revised." Inasmuch as there can be a petition in this court only if approval is denied by the Approving Authority it is difficult, if not impossible, to understand how "such approval" can be "revised" even if that word is construed as "review" as it was in a different statute in Ott v. Board of Registration in Medicine, 276 Mass. 566. It is not so difficult to give effect to the word "revise" as it is used in that portion of the statute which gives an institution aggrieved by an adverse decision of the Approving Authority the right to file a petition "to revise or reverse the decision of the approving authority." Here a construction of the word "revise" as "review" would indicate that the jurisdiction of this court is limited to a re-examination of proceedings already had before the Approving Authority rather than an entire retrial such as would arise on appeal. The point need not be decided, however; because from the outset of the trial before me the parties were fully heard both upon the aspect of a review of the proceedings already had and a trial of the merits of whether Middlesex should be approved or not and because my decision is the same whichever is the proper construction of the statute.

A review of the proceedings of the Approving Authority indicates no reason why its decision should be revised or reversed. A public hearing was held seasonably after the request for approval was filed by Middlesex, which was given due notice of it and was heard without restriction. Within twenty

available spends per year much more than the amount of the tuition, the lowest spent by any of the above three schools being something more than \$800 per year per student. Middlesex, on the other hand, for the year ended June 15, 1944, had a total income, all from tuition fees, of \$190,106.30 and spent \$180,919.10 including the sum of \$45,271.61 for administrative expenses, which is abnormally high compared, for example, with about \$15,000 administrative expenses for Boston University. I am satisfied and so find that, unless there are some unusual circumstances not here present, it is necessary for a medical school to spend an amount in the neighborhood of \$800 per year per student in order to give a proper medical education.

The graduates of Middlesex have in the past year collected some \$50,000 for its use, but only \$5000 has so far been actually turned over to the school. They hope to raise \$50,000 per year hereafter, but so far that is a hope rather than a reality. A parents' association has raised some \$200,000, but this is to be turned over to the school only if it receives approval. Regardless of what the future may hold its necessary financial backing of the school is far below what is necessary to give an adequate medical education.

(2) The quantity of the faculty is not sufficient. The school has in recent years been able to obtain for its teaching staff a number of European refugees who are well qualified in their particular fields. By and large the qualifications of its teaching staff are satisfactory. It is in numbers that it is deficient. At present there are 45 teachers for a student body of about 340. This compares with Harvard having 87 teachers for 525 students, Tufts 433 for 404 students, and Boston University 190 for 255 students. The chief difficulty in obtaining more teachers is again financial. Middlesex uses too high a proportion of its available funds for administrative expenses and does not have sufficient funds to hire a sufficient number of teachers. Clearly 340 medical students cannot be adequately trained by a teaching staff of 45.

(3) The most serious deficiency of all is Middlesex's almost complete lack of clinical facilities for teaching. The modern method of teaching medical students is in great part the observation of sick patients under the guidance of a doctor who is not only a trained practitioner but a teacher as well. In order to do this a medical school must have a connection with one or more hospitals having a sufficient number of so-called "teaching beds." The typical curriculum of a medical school involves for the first year lectures, laboratory work and general demonstrations in hospitals; for the second year the same as the first with the addition of some clinical teaching in hospitals; for the third year almost entirely clinical teaching; and for the fourth year entirely clinical teaching. Frequently, indeed usually, the teacher appointed by the medical school and on its faculty also holds an appointment on the staff of the hospital. Thus he has a double duty — to care for patients in the hospital and to instruct groups of students who go with him as he sees these patients on his rounds. A very large number of "teaching beds" is required both because the small number have to be taught in small groups and because a small number of beds would not produce a sufficient variety of human ailments. Harvard, for example, for its 525 students has 1872 "teaching beds," and Tufts and Boston University on a comparable basis somewhat less. The only hospital with which Middlesex has a similar connection and where persons are paid by it to instruct students at the bedside is the Brockton Hospital, which has a total of 45 "teaching beds." Fourth-year students at Middlesex each have about two weeks' training at this hospital and they also have a short period as "clinical clerks" in a number of other small hospitals. A "clinical clerk" does certain elementary examinations at hospitals and generally assists practicing doctors and interns in those hospitals. Although these "clinical clerks" from Middlesex usually act under the supervision of "clinical preceptors" those persons are not employed by or on the teaching staff of the school and have no actual responsibility for the training of the students. Without doubt these "clinical clerkships" are of value to the student but they fall far short of the value received from organized teaching in hospitals. Middlesex has made strenuous efforts to improve its facilities for clinical teaching but has had little success due to various obstacles not the least of which being the fact that it is not an approved school. The fact remains, however, that at the present time its clinical facilities are grossly inadequate for proper medical education.

days after the hearing it made its decision in writing and notified Middlesex of such decision. The statute requires proving authority to a consideration of such matter as may be brought out in the public hearing. Obviously, it might, from its three previous inspections of Middlesex. From its inspections and study of other medical schools both within and without this commonwealth it had a basis for a comparison of the medical education given at those schools with that given at Middlesex. Two of the members of the Approving Authority are themselves licensed practitioners of medicine and by the very nature of their official positions are presumed to be and in fact are well qualified to judge the kind of education necessary to produce an adequately trained doctor. The third member, although not a specialist in the field of medical education, is a specialist in the field of general education. Both he and the other members of the board are by training and experience far better qualified to pass on the merits of medical education than is this court. They acted fairly and conscientiously and with rigorous regard to the provisions of the statute under which they acted. If this be merely a proceeding to review the proceedings of the Approving Authority its decision must stand.

If the jurisdiction of this court is not limited to a mere review of the proceedings of the Approving Authority but includes an entire retrial of the issue as to whether Middlesex be approved or not the decision must be the same. The statute lays down neither for the Approving Authority nor for this court any guide by which approval should be granted or withheld. Obviously, however, it is designed to make sure that the people of this commonwealth get as good medical care as possible and the fundamental consideration must be that all persons who are licensed to practice medicine are adequately trained for that purpose. It is equally obvious that the purpose of the statute was not to allow as many medical schools to exist (and it is hard to see how one could exist for many years without approval) as there may be students who would like to attend unless such schools give an adequate medical education. The Legislature has recognized that the mere passing of an examination is not a sufficient basis on which to allow one to practice medicine and has therefore provided that a prerequisite to taking the examination must be a proper premedical and medical training. Whether the training which any particular school may give is adequate must in great part depend upon a comparison with the training that other schools give. It must be judged in the light of present-day standards of medical education having due regard to the number of doctors needed to adequately care for the health of the residents of the Commonwealth. Not only the best school or schools are entitled to approval, but somewhere the line must be drawn between a school which is sufficiently adequate and one that is not. A school which years ago might have been the best in the country would not today, had it not kept reasonably abreast of general improvement, be entitled to approval. My decision is, therefore, primarily based upon a comparison with other medical schools concerning which evidence was produced. These were primarily the medical schools of Boston University, Harvard and Tufts.

It would serve no useful purpose to recount these very considerable number of aspects which might, standing by themselves, entitle Middlesex to approval, for there are three aspects in which it is fatally deficient. Nor would it be helpful or material to point out the difficulties Middlesex has had in overcoming these deficiencies in spite of a very genuine attempt in recent years to improve its standards. Nor is it material to consider what it might be in months or years hence even though it be recognized that the very fact of approval would remove some of the obstacles with which the school is faced in its attempt to improve itself. Middlesex, not the Approving Authority or this court, chose the time at which it would seek approval and this court must view it as it now is and not as it has been or may become.

(1) The school has not adequate financial backing. Substantially all of its income is derived from tuition fees paid by students. These are \$450 per year per student, which is not out of line with the tuition fees in other schools, Tufts being \$500, Boston University \$475 and Harvard \$400. But each of these other schools by reason of having other income

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CHARLES C. CABOT  
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(Notices continued on page xvi)

# The New England Journal of Medicine

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MARCH 29, 1945

Number 13

THE YOUNG STETHOSCOPIST\*

REGINALD FITZ, M.D.

BOSTON

School go forward and equally eager for the youth-ful Massachusetts General Hospital to do things. He had been abroad and knew something of the organization of a modern teaching hospital, and no doubt hoped that some day the hospital might attain a high position. Therefore from the very beginning he attempted to make all that he did there as lively as possible, and among other innovations introduced, as promptly as he could, clinical teaching at the bedside.

The teaching at the hospital in those early days also appears to have been conducted on an informal basis. There was but one physician, and one surgeon, on the staff—Jackson and Warren—and also a resident apothecary and house surgeon who were medical students appointed by the Trustees on recommendation by the physician and surgeon. As can be surmised, the presence of medical students "to see the practice of the House" was encouraged so long as they "demeaned themselves correctly and orderly"; clearly a good hospital not only must take care of sick people but must also serve as a teaching center.

It was obvious that the physician and surgeon might be prevented from making ward rounds every day, so provisions were made for appointment of assistants who could carry on the work of their chiefs when necessary. Walter Channing was made assistant physician in 1821, and John B. Brown assistant surgeon in 1823. At first there were only 53 medical and 40 surgical beds in the institution, and during the opening year about 200 cases were followed with the gratifyingly large surgical experience of 40 operations.

In the spring of 1821, the *New England Journal of Medicine and Surgery* published a carefully written review of Laennec's recent book on physical diagnosis.<sup>1</sup> This was an article of more than fifty pages and appeared in the April and July numbers. It ended by stating:

We may be permitted to say that the analysis we have made of this work has cost us much labour. But it would be injustice to Laennec not to say that our review gives a very imperfect representation of the learning and original observations which his work displays. We have already given some opinion respecting the value of the stetho-

WHEN I visited Cleveland a few months ago and looked at the Surgeon General's books housed in the Allen Memorial Library, I happened to meet an old friend. It was a small and unobtrusive volume called *The Young Stethoscopist*, apparently as much at home in Cleveland as in Boston, and now proudly sporting, as if it were a military decoration, the bookplate of the Army Medical Library.

I felt unaccountably pleased that Boston should be represented in such a magnificent collection, and found myself wondering how it happened that a Boston book printed nearly a hundred years ago and as obsolete as a Model T Ford should still be considered of sufficient distinction as to be so beautifully cared for in the Nation's most important medical library.

I found it necessary to go back a long time to discover a plausible answer, back to the days when Bostonians were a race of people dominated by a Brahmin caste, when the State House was the hub of the solar system and when medicine was held firmly in the hands of Harvard College through the unyielding influence of the Warrens, James Jackson and their friends.

The Harvard Medical School in the early nineteenth century had scarcely become established on its own feet, and there was still a good deal of informality in its way of doing things. Yet even when it opened in 1783, John Warren laid plans for the future, and by 1821, when the Massachusetts General Hospital received its first patient, the Warren dynasty was fairly well ensconced: John C. Warren in the chair of surgery, James Jackson in theory and practice, Walter Channing in midwifery, and Jacob Bigelow in materia medica—Brahmins, Harvard College graduates, a closed corporation and as cozy as peas in a pod. The wonder is that the school ever survived such inbreeding.

From an internist's viewpoint, James Jackson was the most interesting member of this group. He was a strong man, eager to see the Harvard Medical

\*Presented at a dinner of the Boston Dispensary, with no trace of self-consciousness, classified its patients racially, as Bostonians, Americans, Hibernico-Americans and Other People.

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Dr. Jackson, Sr., answered:

On the first I received yours of the 28th Oct. It is on the use of the stethoscope, its difficulties. I believe that I wrote you in the same month stating the difficulties on my part. I scarcely expect to overcome them, yet I expect you to do it. It is incomparably easier for you than for me, and you will have great opportunities abroad.

As everyone knows, James Jackson, Jr., died before he had any opportunity to bring to medicine more than great promise. It fell to his successors to accomplish his father's aims.

Henry Ingersoll Bowditch was properly bred to take a part in such a plan.<sup>4</sup> His father was a distinguished scientist and a former Harvard overseer, his mother a Miss Ingersoll and his birthplace Salem. He went to Harvard College and the Harvard Medical School, he served in his student days for a year as house surgeon in the Massachusetts General Hospital, and finally, in 1832, he followed James Jackson, Jr., to Paris.

He stayed in Paris for two years, there coming under the influence of the teachings of Laennec through such masters as Channell, Andral and particularly Louis. He walked the wards with these men, listened to their lectures, copied their mannerisms and for Louis developed the highest admiration. From him he learned three lessons of fundamental importance to his later life: the art of physical diagnosis, the importance of clinicopathological correlation and, above all, the realization that the edifice of medicine reposes entirely on facts that are well and carefully observed.

In Paris, along with Jackson and Holmes, Dr. Bowditch had the honor of election to the Society of Medical Observation. This was a club formed by a group of students under the presidency of Louis. It was the aim of this club to make its members observers of disease. It required each one to go through a kind of initiation in the recording of medical observation, and it demanded that such observations as were made should be submitted to the criticism of the entire membership. Those who belonged were bright and ambitious youngsters. They met each week. They kept notes of what they heard, and each was prepared to pounce on even the most trivial omissions in what the speaker of the evening had to say. Louis summed up their results by criticizing the reader and his critics and by adding anything to the subject under discussion that he chose.

Dr. Bowditch's recollection of his own first performance before this club is still vivid. He recalls his diffidence at attempting to speak in a foreign language at such a gathering, the disparaging attitude of his friends toward his paper and how Louis finally annihilated him by pointing out that his presentation was incomplete since he had discussed only half the subject. Yet experiences of this sort were invaluable and not in the least humiliating; on the contrary, they were inspiring, for although

they were arduous, they were never malicious, they represented honest endeavor, and they were controlled by the guiding hand of a great master. Dr. Bowditch came back to Boston in the fall of 1834. The organization of the Massachusetts General Hospital and the Harvard Medical School was such that no place could be found for him immediately, and so he occupied himself as sort of a voluntary teacher\* until his innings were due. One of the first things that he did was to found the Boston Society of Medical Observation.<sup>†</sup> Its opening meeting was held on March 28, 1835, when Dr. Bowditch and four students organized themselves into "a society for the purpose of collecting and reading detailed observations of cases of diseases as they presented themselves at the Massachusetts General Hospital and elsewhere in Boston." Dr. Bowditch spoke about the parent society in Paris and its usefulness; the members pledged themselves to follow the Parisian model and to meet for two hours one evening each week. At once they elected Louis an honorary member, and before long they were an active club with an increasing list of distinguished members.

Dr. Bowditch took great pride in the society. The early records make interesting reading; it was here that trichinosis was first described in Boston; a curious epidemic of pulmonary disease among horses was studied; and the Massachusetts General Hospital was informed — to its everlasting benefit — that its records were of no particular value from the viewpoint of advancing clinical knowledge. It was here, more than fifty years before appendicitis was named, that a bizarre case was reported concerning a young woman who after breakfast one morning was suddenly seized with a violent colic complicated by chills and fever. As Dr. Bowditch said, the suddenness of the attack, the chills and fever and the colicky pain made the diagnosis difficult. The disorder did not appear to be strangulation of the intestine nor to originate from a diseased liver. What could be the significance of the fact that the region around the cecum was acutely sensitive? It was here that the clinical picture of diaphragmatic hernia was clearly drawn and that thoracentesis of the chest as a means of treatment for hydrothorax was suggested; and it was here on one memorable occasion that Dr. Bowditch read a paper on hippophagy, defending the use of horse meat as an edible viand — perhaps accounting for the existing predilection of the Harvard Faculty Club to serve horse steak at dinner as a particular delicacy. Indeed, the Boston Society for Medical Observation played a part in making medical history.

In 1838, Dr. Bowditch received his first appointment at the hospital and was given a post that was

\*In the catalogues of the Harvard Medical School of that era he is listed as "instructor," which was not a formal appointment. The early records of the Boston Society of Medical Observation are in the Boston Medical Library.

scope. The continued use of this instrument has satisfied us more and more of the benefits which may be attained by it; but we believe it must be used a long while before so much can be ascertained by others, as has been by the inventor. On this point it may be proper to add

In the investigation of the *causes* of dyspnoea, as well as of other symptoms in thoracic diseases, much may be learnt by attending to the effects of position and motion; also by percussion and by *auscultation*, mediate or immediate. . . .

The practice of *percussion* is founded on the following circumstances. When the air is admitted fully into the lungs, the thorax resounds on percussion like a hollow cask, with the exception of certain regions. When the air is not permitted to enter any particular part of the lungs, a blow over that part will produce a flat sound. The extent, over which this flat sound is perceived, will determine the extent to which the air-vessels are compressed or obstructed; and if the compressing cause be moveable, such as a fluid in one of the cavities of the pleura, this may be discovered by attending to the effects of a change of position, as regards the parts affording the flat sound.

The use of the *stethoscope* is founded on the following circumstances. The motion of the air in the lungs, with all the obstacles to the regular passage of it, is productive of sounds, which may be heard by placing the ear on the chest. So also is the motions of the heart capable of being ascertained by the ear. But these sounds in the thorax may be ascertained most conveniently through a cylinder of wood or of other material; one end of the instrument being rested on the chest, and one end being applied to the ear. When such an instrument is used the auscultation is mediate; when the ear is applied to the thorax the auscultation is immediate. If the instrument be applied when the patient is speaking, a tremor is perceived over healthy lungs; but when the lungs are diseased, or compressed, the changes are manifested by certain peculiar changes in the sounds transmitted through the instrument.

It would certainly be very useful to distinguish during life, the different organic changes [in the heart]. . . . We can however with some degree of assurance, distinguish the following affections, viz: hypertrophia of the heart, dilatation of its cavities, and these two combined. In making these distinctions, much aid may be derived from the use of the stethoscope. We may also sometimes distinguish diseases of the valves and aneurism of the aorta. Dropsy of the pericardium is not easily distinguished.

For a teacher growing no younger year by year and with hearing becoming less acute, it was excessively hard to improve one's skill in physical diagnosis by the method of self-teaching. The obvious answer was to send to France to learn the new technic a procession of Bostonians from the right kind of families so that, as Dr. Jackson expressed it, these young men when they returned could put their ears in use at his hospital.

The leader of this procession was James Jackson, Jr., who left the medical school as an undergraduate in 1831; he was soon followed by Henry Ingersoll Bowditch, Oliver Wendell Holmes and Mason Warren. There is something appealing about young Jackson's first letter home and his father's reply to it.† From Paris, shortly after he arrived there, James Jackson, Jr., wrote:

I feel almost disposed to cover a sheet or two in enumerating the difficulties of auscultation. If Laennec has added an important aid to our insufficient means of exploring diseases of the chest, he has, at the same time, rendered the study of those diseases more difficult, more laborious I would say, to the learner. . . .

By the by, you would be much surprised, my dear father, to see how much more the immediate auscultation is used here, than the mediate. There is one other point, we are too apt to neglect at the M. G. H. It is the examination of the dorsal region. The French examine the back more than the front; we do the contrary; both err, but they the least.

†Many delightful letters between James Jackson, Jr., and his father can be found in Putnam's *A Memoir of Dr. James Jackson* (Boston and New York: Houghton, Mifflin and Company, 1906) and in Jackson's *A Memoir of James Jackson, Jr., M.D.* (Boston: I. R. Butts, 1835).

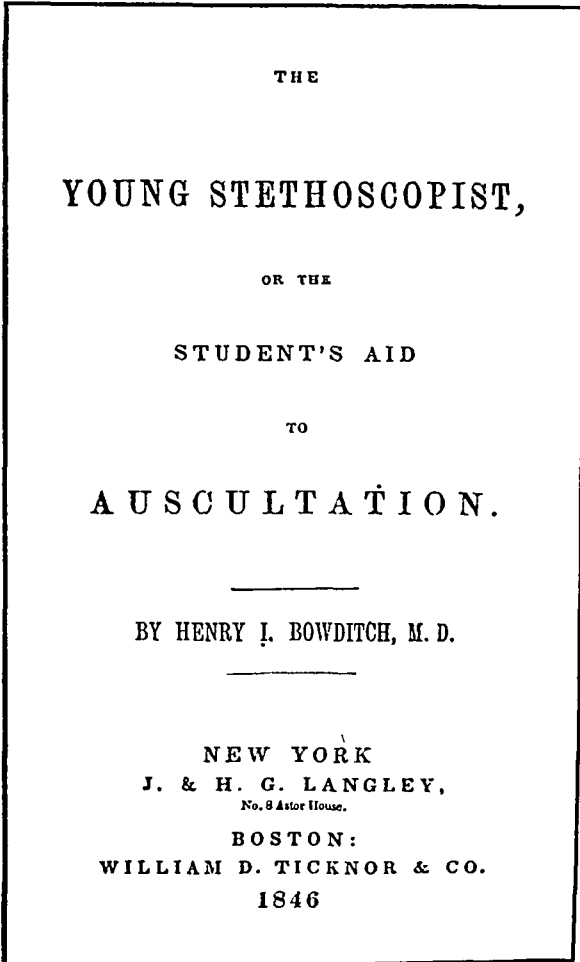


FIGURE 1. Title Page from *The Young Stethoscopist* (Harvard Medical Library).

that much must depend on the perfection of the sense of hearing. A man with a nice ear for music would probably discover much more by this instrument than one who has not that organ so delicately constituted.

Obviously someone in Boston obtained a copy of Laennec's book shortly after its publication and started to work on physical diagnosis by his methods. The review\* is unsigned, and the owner of the original copy that was the pioneer in Boston cannot be identified. It is known, however, that Dr. Jackson was much interested and that as soon as possible after this review was printed he began to teach auscultation and percussion in the Harvard Medical School. To prove this, in 1827 there appeared from his pen for the use of his students a textbook on the theory and practice of physic.<sup>3</sup> He has some interesting things to say about these methods.

\*There is a hint in it that Dr. Jackson wrote it, for he appears to have found auscultation a difficult art. In a letter dated March 5, 1833, he said, "My ears are old and were not trained early."

a little noise around Boston. To poke fun at it in the midst of a group of intimate friends would have amused Dr. Holmes, would have been timely and was the sort of thing he knew how to do so well and gracefully.

The tune that was used is lost, but the words remain. The story of the song is simple enough; it is about a young Boston doctor who procured a new stethoscope, with an ivory cap and a lovely polish. Unfortunately a couple of flies housed themselves in it so that whenever he used the instrument he heard noises that would have perplexed Laennec; and he made improbable diagnoses that were invariably wrong. At last six young maidens, who were growing pale and had taken to sighing or to eating such things as coal or chalk, consulted him. Naturally, because of his zeal in using the stethoscope, the young doctor was not interested in anything so commonplace as looking at them, but he heard such ominous buzzings in their chests when he listened that he felt sure they all must die. However, before this happened, six young men fell in love with the maidens and married them, and at once they grew well.

**D**URING the course of each year, a number of patients suffering from dermatitis exfoliativa caused by the arsenphenamines are treated in the dermatologic wards of Bellevue Hospital. Most of these patients have been treated for syphilis by private physicians, hospital clinics or public-health services in New York City. The 50 cases reported herein were observed at Bellevue Hospital between the years 1937 and 1942, showing that the dreaded postarsphenamine dermatitis is not rare even in the present period of antisyphilitic therapy. These patients were studied in the dermatologic wards from their admission until they were well enough to leave the hospital. Three of the patients had received their antisyphilitic treatment in this hospital.

The histories of these cases furnish convincing evidence that this complication of treatment could have been avoided in a number of cases, and that in the 2 fatal cases death might have been prevented if it had been possible to obtain a proper history and if the warning signs had been recognized.

From the Department of Dermatology and Syphilology, New York University College of Medicine, and the Department of Dermatology and Syphilology, Third Medical Division, Bellevue Hospital (care of Frank C. Coombs, M.D.).

Assistant clinical professor of dermatology and syphilology, New York University College of Medicine; assistant attending dermatologist and syphilologist, Third Medical (New York University) Division, Bellevue Hospital.

Senior resident, Third Medical (New York University) Division, Bellevue Hospital.

## DERMATITIS EXFOLIATIVA FOLLOWING ARSPHENAMINE THERAPY\*

### Observations on Fifty Cases

Maurice J. Costello, M.D.,† and SIMMON LANDY, M.D.‡

NEW YORK CITY

The ages of the patients ranged between eighteen and sixty-nine years. There were 3 in the second decade, 9 in the third, 12 in the fourth, 16 in the fifth, 8 in the sixth and 2 in the seventh. The average age was 38.5 years.

There were 26 women and 24 men. Twenty-six were Negroes, 22 were Whites, and 2 were Japanese. Nineteen occupations were represented. Housewives, restaurant workers and unemployed constituted over 60 per cent of the total number. The average hospital stay was forty-three days, the shortest four days and the longest one hundred and seventy-one days. The average duration of the arsenical dermatitis was sixty-nine days, the shortest ten days and the longest two hundred and forty days. Forty-eight patients were improved or cured, and 2 died.

When admitted to the hospital for treatment of the arsenical dermatitis, 1 patient was in the primary stage of syphilis, 34 were in the secondary stage, 3 had early latent syphilis, and 11 had late latent syphilis. None of the patients had manifestations of tertiary syphilis. One patient had a papulo-necrotic tuberculide.

Forty-two patients had received neoarsphenamine, 2 had received Mapharsen, 2 had received Mapharsen followed by neoarsphenamine because they developed a mild dermatitis from the former, and 2 had received acetylsalicylic acid.

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In these days when we have, besides the stethoscope, the x-ray, the cardiogram, a method for visualizing the heart sounds, new drugs, allergy, blood chemistry and metabolism tests, all combining to make diagnosis complicated and common sense obscure, the last verse of the "Stethoscope Song" is worth remembering.

Now use your ears, all you that can,  
But don't forget to mind your eyes,  
Or you may be cheated, like this young man,  
By a couple of silly, abnormal flies.

probably more to his taste than any other. The hospital had grown considerably since it opened and since that memorable day in 1825 when General Lafayette, accompanied by the governor and the lieutenant governor, had driven to the Bulfinch Front and after being properly received by the president and members of the Board of Trustees, flanked by the physicians and surgeons, inspected the building. Business was so brisk that an admitting physician had proved necessary, a doctor who would see the patients before entry, determine their condition, decide whether they were properly admissible, do whatever outpatient work was indicated and, more important still, be responsible for all pathological examinations of the institution. Dr. Bowditch felt pleased to receive this appointment, for it gave him an opportunity to put into practice some of his Parisian training. One of his students said that he now regularly spent an hour each morning examining patients, at the same time teaching physical diagnosis and giving his young assistants every opportunity to practice this art.\* If an autopsy was to be performed, he would devote the entire afternoon to it, appointing a student assistant and making the medical house pupil take notes from dictation so that the record might be as complete as possible.

Apparently this method of teaching met with the approval of the president and fellows of Harvard College. For the catalogue of 1841-42 for the first time announced that the course in medicine embraced lectures given at the medical college on the general principles of pathology and treatment and clinical lectures given at the Massachusetts General Hospital. The latter were given twice a week and occupied two hours each. The catalogue states, "Students have an opportunity of visiting all the cases and of observing and learning the symptoms and treatment of each case and particularly of the exploration of the body for the physical signs of disease by *palpation, auscultation and percussion*." In this fashion the use of the stethoscope was finally made respectable in Boston and all students were taught how to use it.

Any teacher who has a hand in developing a new course at the Harvard Medical School is likely to wish to prepare his own textbook. It is not surprising, therefore, that in the summer of 1844, Dr. Bowditch wrote a friend: "I sit most of the time in the front parlor preparing my book on auscultation, which I believe I am fairly engaged in now," nor that in December, 1845, the *Boston Medical and Surgical Journal* prepared a welcome for *The Young Stethoscopist*. "We understand," it stated, "that Dr. Bowditch of this city, has in press a new work, under the above title, on the Physical Signs of Diseases of the Chest. It is intended as an aid to students, and to physicians resident in the coun-

try. About the middle of January it will, probably, be ready for the trade."

*The Young Stethoscopist* came out on time, a slim volume full of wisdom and practical hints on how to examine the chest properly. Henry J. Bigelow<sup>†</sup> reviewed it shortly after its birth and remarked of Bowditch and his work: "He has booked Laennec up to date and has compressed his genius, as the fisherman in the *Arabian Nights* did his, into a prodigiously small volume. We commend it to auscultors and to non-auscultors."

*The Young Stethoscopist* proved popular and went through two editions. It is one of the first books on auscultation and percussion by an American writer to be published in this country, and it has an interesting background, relating together Laennec, Louis, the Jacksons and through them all subsequent American auscultors. For these reasons it is more than a bibliographic curiosity and has well earned a place in the Army Medical Library. Besides this, there is reason to imagine that the book is unique: as a possible appendage, it has a humorous Back Bay postscript that forever makes its contents point a significant moral to young stethoscopists.

The Boston Society for Medical Improvement was established in 1828.<sup>6</sup> It started simply — a gathering of colleagues who met regularly to talk shop. But from the beginning the society developed a delightful tradition that I am pleased to observe has been copied by the Honorary Consultants to the Army Medical Library — the tradition of an annual dinner. The dinner was an occasion of geniality where men talked and laughed, sang songs or even poetized if the spirit moved them. When Dr. Holmes was secretary he left a pleasant account of what went on:

At seven o'clock the Society disposed itself at table animated by the presence of the dinner, which, by its outward arrangement and intrinsic excellence, did honor to the taste and judgment of the provider. . . . No incident occurred to interrupt the festivities of the evening, with the exception that a couple of our most efficient members were interrupted for a short time by accidents too frequent on these occasions. An amiable indiscretion, dating undoubtedly from some bright May morning, was visited upon the heads of Drs. Ware and Adams, by a midnight call into the midst of a February snowstorm. The hilarity of the company was temporarily diminished, and the census of the city permanently increased during their absence.

As the years rolled by, the annual dinner came to be anticipated with increasing eagerness; one was sure of a good meal, an evening of relaxation, speeches that were neither too long nor too dull and a poem by Dr. Holmes.

It was at the dinner in February or March of 1846,<sup>†</sup> I suspect, that Dr. Holmes introduced the "Stethoscope Song." *The Young Stethoscopist* was then brand new but already old enough to have made

\*Dr. Bowditch still had no formal appointment in the medical school so that his teaching must have been largely a voluntary effort.

<sup>†</sup>This date is a matter of guesswork. No student of Dr. Holmes has determined accurately when the "Stethoscope Song" was written or first sung. T. F. Currier, who knows as much as anyone about the matter, says that its first printed appearance, so far as he can ascertain, was in the 1849 edition of the doctor's poems, which appeared in November, 1848.

Twenty-five of the patients had a temperature of over 100°F. The highest temperature was 101°F. in 9 cases, 102°F. in 4, 103°F. in 8 and 104°F. in 3. One patient had a temperature of 105.6°F. Even moderate fever was accompanied by malaise and prostration.

Clinical jaundice occurred in 2 patients. In a patient with latent syphilis, it preceded the eruption by three days. The patient had received four injections of neosarsphenamine. The icteric index was 9, the van den Bergh direct reaction was delayed, and the indirect reaction was positive. The other patient had been treated several years before. The icteric index was 9, the van den Bergh direct reaction was slightly positive. Urinalyses did not show abnormal findings in the majority of the patients. Albumin, casts and white or red cells were occasionally found. A + test for sugar was noted in 1 patient. The urines of 10 patients were examined for arsenic. In 6 patients, the amounts per liter varied from 0.004 to 1.540 mg.; in 2, arsenic was said to be present; in 1, there were varying amounts; and in 1, a +++ test for arsenic was reported.

Twenty-seven patients had a positive blood Wassermann reaction and 23 a negative reaction. In the great majority of the cases studied, the eruption was generalized or universal. The regions of the body affected, in the order of frequency, were as follows: extremities, torso, axillae, groins, neck, face, chest, back, eyelids, hands, feet, ears, wrists, ankles, scalp, lips, oral mucous membrane and conjunctivas. Generalized adenopathy was present in most of the cases.

It is well known that the arsenical drugs are capable of causing many types of toxic cutaneous manifestations; of these, dermatitis exfoliativa is the most serious. Pruritus, burning and pain in varying degrees were common to all the eruptions. Erythema, scaling and severe exfoliation occurred in nearly all the patients. Edema, especially of the lower extremities, due to stasis, and angioneurotic edema of the eyelids, face, lips and mucous membranes were constant features of the early manifestations of the dermatitis. Denuddation of the mucous membranes of the mouth and respiratory tract, causing severe bronchitis, was frequently encountered.

The eruption began with the appearance of flexural erythema and pruritus, followed by large coin-sized, dusky red, slightly elevated lesions on the torso, especially the back. These lesions often resembled those of erythema multiforme and by lessened.

Feeling of the palms and soles, accompanied by pruritus and fever, were occasional forerunners of the severe generalized eruption. In many cases, if these signs had been heeded, the generalized dermatitis might have been prevented or its gravity lessened.

Intravenous glucose solution was administered to 10 patients in daily amounts varying from 20 to 50 cc. of a 50 per cent solution for ten days. Glucose administered in this manner appears to be questionable value.

Sodium thiosulfate was administered intravenously to 30 patients. The smallest number of injections was three, the highest ten and the average four. These patients also received 1 gm. of sodium thiosulfate by mouth three times a day for ten days. This drug was of no value, which agrees with the clinical experience of Allore and the experiments of Allore,<sup>5</sup> who investigated the effect of sodium thiosulfate in the treatment of arsenical poisoning in rabbits. One gram of calcium gluconate was administered intravenously to 10 patients every other day for six doses. It was of questionable value.

Complete blood-cell counts were performed on many of the patients, and in most cases they were within normal limits. In a few cases the red-cell count was as low as 2,500,000, and in several it averaged about 3,500,000. A number of patients had a low hemoglobin; in several cases it was between 50 and 60 per cent. One patient had thrombocytopenia, the blood platelet count being 60,000. Leukocytosis was more frequently encountered than eosinophilia was frequent, the percentage ranging from 10 to 56, but severe injury to the bone marrow resulting in agranulocytic angina and purpura was not observed.

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mine. The type of arsenical administered to the remaining 2 patients was unknown.

The smallest number of injections administered prior to the development of dermatitis exfoliativa from neoarsphenamine was three and the largest sixteen, with an average of eight. The majority of the patients complained of pruritus or dermatitis soon after the fifth, sixth or seventh injection. In many cases either these warning signs were not observed or the patient was not questioned concerning them. Ignorance of the significance of mild itching and mild dermatitis in the course of arsenical therapy led to full-blown dermatitis exfoliativa.

One of the patients had pruritus after the third injection. This increased until it was accompanied by dermatitis after the seventh injection, and death followed soon after the tenth injection. Another patient, who developed a severe dermatitis exfoliativa after the first injection of neoarsphenamine, later gave a history of having had a similar eruption eleven years before that had required hospitalization for two months; the eruption followed the third injection of an arsenical preparation. It began as generalized urticaria and angioneurotic edema of the face and lips and was characteristic of the dermatitis that occurred in those who had previously been sensitized. This severe complication of arsenical therapy can usually be anticipated, but several of the histories show that in patients sensitized by previous injections of an arsenical preparation the eruption appeared after the first injection of the arsphenamine.

Another patient received one injection of neoarsphenamine and developed a severe dermatitis exfoliativa with numerous vesiculobullous lesions. She had received about seventy-five injections of neoarsphenamine in 1935 and 1936, which was three years prior to the eruption on admission.

A patient stated that he had received a course of neoarsphenamine followed by a course of mercury sixteen years previously, without untoward effect. After the second injection of neoarsphenamine in the series of treatment before entry, a mild dermatitis appeared. He did not report this until he had received six injections of neoarsphenamine, when a generalized pruritic exfoliating dermatitis was present.

Another patient tolerated well his first course of an arsphenamine and two courses of bismuth salicylate, but developed a moderately severe dermatitis following the first injection of the second course of neoarsphenamine.

One injection of neoarsphenamine was administered to a patient in 1920, and he received no further treatment until 1941, when he developed an eruption of a mild nature following the fifth injection of Mapharsen and a dermatitis of severe character after subsequently receiving two doses of neoarsphenamine—0.2 and 0.4 gm., respectively—at weekly intervals.

Robinson and Moore<sup>1</sup> have induced a second attack of dermatitis with a very small dose of arsphenamine—0.1 cc. of a 1:2000 solution—injected intradermally six years after the first eruption.

One patient developed an eruption after having received twelve injections of Mapharsen. The dermatitis was mild, and intravenous injections of neoarsphenamine were substituted for Mapharsen. After the fifth injection of the latter drug, the patient developed generalized pruritus, and after the sixth injection a lichen planuslike eruption on the wrists and ankles. Later the eruption became generalized, exudative and fissured and was accompanied by edema of the face and severe itching. It is probable that Mapharsen sensitizes such patients to the neoarsphenamine subsequently administered.

Mapharsen was the cause of an arsenical eruption in 2 patients, to whom it was the only arsphenamine administered. In one of them, the dermatitis appeared after the twenty-first injection; in the other, it appeared after the sixteenth injection. Mapharsen seldom causes an arsenical dermatitis. When it does, the eruption usually appears late, unless the patient has been previously sensitized.

Acetylglucoarsphenamine, administered by intramuscular injection, was given to a selected group of patients in the dermatologic wards of Bellevue Hospital. One patient after the sixth injection of this drug developed pruritus and a mild dermatitis, which became aggravated and more extensive after the seventh injection. Another received ten injections of acetylglucoarsphenamine before the eruption appeared.

Intramuscular injections of bismuth salicylate and intravenous injections of an arsphenamine were administered in alternating courses to 12 patients. In 10 cases these drugs were given concurrently, that is, the heavy metal was administered in the same week as the intravenous injection of the arsenical drug. Twenty-eight patients received only the arsenical drug without the heavy metal. It appeared to make little difference whether the arsphenamine was administered with a heavy metal in alternating courses, concurrently or alone. When it was administered in alternating courses with a heavy metal the eruption appeared, on the average, following the ninth injection; when it was given concurrently, after the eighth injection; and when administered alone, after the sixth injection. This leads one to believe that the extra load of heavy metal therapy is not a factor in the production of arsphenamine dermatitis exfoliativa.

All the patients who developed an eruption following the first or second dose of an arsenical preparation gave a history of having previously received an arsphenamine. Moore,<sup>2</sup> and Stokes,<sup>3</sup> whom he quotes, state that they have seen patients who developed exfoliative dermatitis after the first dose of an arsenical preparation.

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## MEDICAL PROGRESS

### INSECT VECTORS OF DISEASE (Concluded)

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#### CONTROL OF INSECT-BORNE DISEASES

Space does not permit complete discussion of the control of various types of insect-borne diseases. There are, however, certain factors that apply to most of these diseases.

In the normal course of an epidemiologic investigation, collections are made of the insects suspected of transmitting the disease in question. The best method for collecting insects is to take advantage of their feeding habits. Adult mosquitoes may be collected either while biting man or while resting on walls and ceilings.<sup>1</sup> A large glass test tube, containing rubber bands saturated with carbon tetrachloride or chloroform at the bottom is placed over the specimen until the mosquito is anesthetized. Then it is slowly removed and the tube corked with the specimen inside the tube. After an interval of a few minutes the specimen is carefully placed between layers of cotton batting in a suitable container, such as a pillbox, and properly labeled. The following data should always be noted at the time the specimen is captured: place of capture—state, town, street and number of house or location of barn, description of surroundings and so forth; date, time of day, climatologic conditions and so forth; remarks regarding conditions when caught, such as biting man or horse, where resting and so forth; and name and address of collector. When mosquito larvae are collected, similar data should be noted,<sup>2</sup> particularly the type of body of a suction bulb and are put into test tubes containing 70 to 80 per cent ethyl alcohol or 10 per cent formalin. Each tube should be properly identified, preferably by placing a slip inside the tube. Bugs and ticks should be removed by forceps, as crushing the arthropod between the fingers may result in infection of the collector. Specimens

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should be immersed in 70 per cent ethyl alcohol containing 1 per cent formalin. Large specimens, after killing with chloroform or carbon tetrachloride, may be transfixed by pins and mounted in a box. Sucking lice are found only on their host. Nits are most easily collected from animals. Fleas may be collected both from animals and their nests. Specimens can be preserved in 70 per cent ethyl alcohol.

Two groups of arthropod-borne diseases, namely, those that are transmitted by mosquitoes, chiefly malaria, and the typhus fevers, which are transmitted by lice, mites and fleas, will be used to illustrate the methods of attack against these diseases.

#### Mosquito-Borne Diseases

The malignancy with which malaria can attack an area is illustrated by the spread of the disease in Brazil after the introduction of *Anopheles gambiae* from Africa by either ship or airplane.<sup>3</sup> In 1937 and 1938 it caused an epidemic in one section that affected some 60,000 out of a total population of 70,000 and caused over 5000 deaths. Vast sums of money were expended by the Brazilian government and the Rockefeller Foundation in an attempt to exterminate *A. gambiae*,<sup>4</sup> which threatened only to pauperize Brazil but to extend throughout South America and perhaps even farther. Until quite recently it was believed that this vector had been eliminated from Brazil, but it has again been found, probably being a reimportation.<sup>5</sup>

Briefly, the control of any mosquito-borne disease must be based on one or more of the following procedures: control of the mosquito vector; protection of man and animals from the bites of infected mosquitoes; immunization of susceptibles; removal of sources of infection of mosquito vectors; and, finally, prevention of entry of the mosquito into areas unaffected by the disease. All these methods are not applicable to every mosquito-borne disease. *Mosquito control*. Certain conditions are necessary before a mosquito-borne disease can become

of benefit in detoxifying the patient. Mu<sup>6</sup> thinks that there is an association between liver damage and glucose metabolism. It was necessary to give blood transfusions to 3 patients because of severe secondary anemia.

Concentrated vitamin preparations, including ascorbic acid, 100 mg. three times a day, were administered. It was impossible to determine their value because they were not administered alone. Seven patients received intramuscular injections of crude liver extract. In several cases this form of therapy had to be abandoned because the patient developed deep abscesses that had to be widely incised and drained. Hence, patients suffering from exfoliative dermatitis should not be given crude liver extract intramuscularly because of the likelihood of abscess formation at the contaminated sites of injection.

It was necessary to administer sedatives to many of the patients because of the nervousness and loss of sleep occasioned by intolerable itching and burning. Patients were encouraged to drink copiously of fluids, especially fruit drinks.

Local treatment in general consisted of the following: potassium permanganate, starch and colloid baths; body inunctions with boric acid ointment; and wet compresses of a 1:10 Burow's solution. Other forms of local therapy were applied, depending on the indications that arose. Dalibour's solution (1:10) was applied as wet dressings and was also used in the bath. Wet boric acid compresses and wet dressings of silver nitrate solution (1:1000) were of value in treating areas of secondary infection. Aquaphor and lime-water ointment proved to be a good emollient. Ten per cent oil of cade in aquaphor relieved the pruritus in the dry stage of the eruption. Forty per cent sulfur ointment was of little value. A 1 per cent alcoholic solution of brilliant green proved efficacious on moist, oozing areas, such as the axillas and inguinocrural regions. Crude coal-tar paste was of value in the patchy dry areas that remained when the universal eruption was undergoing involution.

The application of Unna boots was helpful in patients who had uncontrollable itching and severe edema of the lower extremities. The application of subfractional doses of superficial roentgen rays had no appreciable effect on the pruritus or the dermatitis.

The following recommendations are based on the clinical findings in this series:

The patient should be asked at each visit whether he has itching, a rash, fever or headache.

When arsphenamine, neoarsphenamine or silver arsphenamine has been used, it is advisable to have the patient remove his clothes for a complete examination of the skin before the sixth, seventh and eighth injections. A similar examina-

tion should be performed before the twelfth to the fifteenth injection of Mapharsen.

If a patient develops an eruption that is not readily recognized as one caused by the arsphenamines, it is safer to withhold treatment until a dermatologist decides the question.

The patient should always be asked, regardless of the stage of the syphilitic infection, whether he has previously received intravenous or intramuscular injections. Information on this point may modify treatment and thus prevent the explosive reaction following the first dose of an arsphenamine drug in a sensitized person.

Further treatment with an arsenical preparation should never be given if the original dermatitis was vesiculobullous or exfoliative. Disregard of this warning may be fatal. Subsequent treatment with an arsphenamine is also dangerous if it produces a macular, maculopapular or lichenoid exfoliating eruption with pruritus. If treatment with an arsenical drug is imperative in this group, all vestiges of the dermatitis must have disappeared before an arsenical drug in small doses is again cautiously administered. Reappearance of the dermatitis following this procedure should forever contraindicate the administration of the arsphenamines.

It is advisable to examine the urine daily during the course of dermatitis exfoliativa and to conduct a complete examination of the blood frequently in the acute phase, because blood dyscrasias are at times associated with the former complication.

#### SUMMARY AND CONCLUSIONS

The observation and treatment of 50 patients with dermatitis exfoliativa caused by the arsphenamine drugs are discussed. Recommendations regarding therapy that are based on these observations are given.

Age, sex and race apparently played no part in the causation of arsenical dermatitis.

Freedom from reaction to arsphenamines at a previous time does not guarantee the same good fortune with future arsenical treatments.

Major arsenical dermatitides are extremely resistant to all forms of general and local treatment, including the application of superficial roentgen rays.

The major arsphenamine dermatitides have certain features in common: they are pruritic; they are generalized or universal; they are exfoliative, with constitutional symptoms and evidence of injury to the viscera, especially the liver; and they are made worse by the continuation of arsenical therapy.

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hour. Dimethyl phthalate is intermediate in lasting qualities. Repellents must be applied to all exposed surfaces except the mucous membranes. Certain species of Anopheles prefer animal blood to that of man. In areas where such mosquitoes are vectors, they may be diverted by the importation of animals. This zoophilic attraction to cattle has been used in the Balkans.

#### *Immunization of susceptibles.*

It is, however, not yet available to the public in all endemic areas. Although the vaccine is a live attenuated virus, no case of typical yellow fever has resulted from over two million vaccinations performed in Brazil.<sup>14</sup> Furthermore, it has been demonstrated that mosquitoes that bite vaccinated persons did not infect monkeys on subsequent biting. Unfortunately, immunity is temporary and annual revaccination is required.

In equine encephalomyelitis, a vaccine composed of formalized virus obtained after growth in chick embryos has proved effective in the protection of horses.<sup>15</sup> Except for laboratory workers, this vaccine has not been used in man, owing to the severe reactions that have been encountered. Moreover, the risk of exposure to the disease has been so small that community immunization has not been indicated. Vaccination of horses must be repeated annually, since the immunity is temporary. The decrease in the incidence of this disease since 1939 has been attributed in part to the vaccination of horses.

There is no specific immunization against the other mosquito-borne diseases. The suppressive use of quinine<sup>16</sup> and Atabrine<sup>16</sup> in malaria is an attempt to destroy the plasmodium as soon as it is introduced into the blood stream. Neither drug,<sup>17</sup> however, is effective in preventing the disease. The activity of the plasmodium is reduced while suppressive doses of the drug are being administered, but about two weeks after such doses are stopped, symptoms of clinical malaria are likely to make their appearance. There is some evidence that the prolonged use of suppressive doses of both quinine and Atabrine, which are about equally effective, tends to lessen the seriousness of malaria in subsequent attacks. Plasmodium is of no value as a suppressive drug in malaria.

There is no general cross immunity in malaria, nor are there any between types or even different strains of the same type. This was well illustrated by failure of the British attempt to forestall malaria in Malaysia by using Indian troops who had previously had malaria.<sup>18</sup>

*Removal of sources of infection.* This is effective only to a limited extent. Cases of the disease, with the infecting agent in the circulatory blood, may act as foci of infection for vectors. Theoretically, it is therefore good preventive medicine to isolate

#### *Typhus fevers*

The typhus fevers comprise a group of diseases entities each with its peculiar epidemiologic setting.<sup>19</sup>

Classic European or epidemic typhus fever is louse transmitted,<sup>19</sup> and all measures that are employed to delouse achieve a measure of control of the disease. The older methods of delousing bodies and clothing<sup>20</sup> are familiar to all veterans of World War I.

When control methods are dependent on control of man, only limited success may be expected, as some individuals are unco-operative. The most effective method in the control of mosquito-borne diseases has been a direct attack on the mosquito, which results in a reduction of vectors to a point below the critical level required to maintain the disease.

Persons, however, several instances are recorded in which disease vectors and other insects have been transported to areas where they had never been found.<sup>19, 21</sup>

Since the hosts include animals and birds, the geographical limitation of this disease becomes a difficult problem. Malaria and filariasis are usually spread by hosts who are not known to be infected, and in these days of rapid transportation it is practically impossible to eliminate the travel of such persons.<sup>22</sup> Moreover, several instances are recorded in which disease vectors and other insects have been transported to areas where they had never been found.<sup>19, 21</sup>

encephalomyelitis has an even wider host selection. Its spread may be due to vectors or hosts. Since the hosts include animals and birds, the geographical limitation of this disease becomes a difficult problem. Malaria and filariasis are usually spread by hosts who are not known to be infected, and in these days of rapid transportation it is practically impossible to eliminate the travel of such persons.<sup>22</sup> Moreover, several instances are recorded in which disease vectors and other insects have been transported to areas where they had never been found.<sup>19, 21</sup>

*Prevention of entry into new areas.* This method is applicable to all arthropod-borne diseases. The principles of isolation and quarantine<sup>23</sup> are utilized in every community. In the case of certain diseases, especially those with a wide host selectivity, the prevention of the spread of a disease is difficult. This feature is well illustrated by yellow fever. This disease was apparently controlled in Brazil by the use of the usual mosquito-control methods and isolation and quarantine on a community basis.<sup>15, 24</sup> Suddenly, however, it became apparent that jungle yellow fever was due to the persistence of the disease in other hosts and vectors.<sup>15</sup> Equine encephalomyelitis has an even wider host selection. Its spread may be due to vectors or hosts. Since the hosts include animals and birds, the geographical limitation of this disease becomes a difficult problem. Malaria and filariasis are usually spread by hosts who are not known to be infected, and in these days of rapid transportation it is practically impossible to eliminate the travel of such persons.<sup>22</sup> Moreover, several instances are recorded in which disease vectors and other insects have been transported to areas where they had never been found.<sup>19, 21</sup>

epidemic or reach a high endemic index. One of these is the existence of a certain numerical relation between hosts, vectors and susceptibles. When this numerical relation is upset by a reduction of the number of vectors, the disease ceases to be epidemic and rapidly declines, either arithmetically or geometrically, depending on the interrelation of many related factors. It becomes apparent that a moderate reduction in the number of mosquitoes below the critical level will markedly reduce the prevalence of the disease in an area where there are many persons who are immune, but in a region with many who are susceptible, the reduction below the critical level must be much greater. This concept was developed many years ago by Ross, who applied it to malaria; Carter and Gorgas applied it to yellow fever.

The bionomics of mosquitoes are such that control measures must be designed to eliminate or control the larvae or the adults. The measures that are most effective in any area depend on local factors and on the genus and species of the mosquitoes concerned. It is impractical and uneconomical to attempt to control all mosquitoes. The control measures must be directed against that species which it is desired to reduce below the critical level. Therefore, in order to ensure effective control measures, it is important to understand the bionomics, breeding habits and seasonal and geographical distribution of the species that are concerned with the transmission of the disease. Since local circumstances vary, it is necessary that a mosquito survey<sup>51, 137</sup> be made before control measures are introduced into any area for the purpose of controlling mosquito-borne disease. Even in controlling mosquitoes as a nuisance, it is necessary to determine their bionomics before an economical and efficient nuisance control can be expected.

Mosquito control has been effective in malaria and yellow fever. There has been considerable less experience in the effectiveness of this method in dengue fever, but since the principal vector of this disease is the same as that of yellow fever, there is every reason to believe that mosquito control will prove just as effective. In filariasis this method has also proved to be effective where it can be applied. To date, there has been no notable effort to control the vectors of equine encephalomyelitis. Theoretically, this method should be effective; but the natural vector of this disease has not yet been determined, and additional epidemiologic and entomologic investigations are needed before this method can be applied.

Mosquito control measures are of two types—temporary and permanent<sup>138</sup>; to these may be added natural control, such as surface-feeding fish. Temporary measures consist of the application of larvicides, such as oils, Paris green, other dusts and, finally, D. D. T. (dichloro-diphenyl-trichloro-

ethane). Larvicides are used whenever permanent control is either not possible or not economical. The best larvicidal oil kills in less than thirty minutes and consists of No. 2 fuel oil. It kills by suffocating the larvae by blocking the respiratory tubes, the toxic action of the volatile oils and vapors, the toxic action of the water-soluble fraction and the change in surface tension whereby the larvae cannot remain attached to the water surface. The oil is applied by sprays, at a rate of about 15 gallons per acre at intervals of seven to ten days. Paris green is usually diluted with other dusts so that the final mixture contains 2.5 to 5 per cent Paris green by volume; it is applied by a rotary blower using  $\frac{1}{2}$  to 1 pound of Paris green per acre at weekly intervals. It is especially active against anophelines, being an intestinal poison that floats on the surface and is easily available to the top-feeding larvae.

Permanent control measures may include drainage, channeling of streams and marshes, filling, shore-line cleaning and removal of vegetation, periodic water-level fluctuation, flooding, flushing and automatic syphoning, changing water salinity, shading or exposing to sunlight and introducing natural enemies. Their application depends on the terrain, the species to be controlled and the cost and effectiveness of the types of control measures available. Only an expert malariologist should attempt to decide on proper permanent control measures.

*Protection from mosquitoes.* Effective protection from the bites of mosquitoes can be accomplished only under extremely limited conditions. Screening, the use of nets and the avoidance of unnecessary exposure are the most effective methods. Spraying in houses, the application of mosquito repellents<sup>139</sup> and the killing of individual adults are adjuvants. For this method to be really effective, animals and man would have to remain behind screens at all times. Since this is a physical impossibility, protection against mosquito bites is only partial. It is about equally applicable in all mosquito diseases, the differences being dependent on the habits of the adults of the species concerned.

Military units moving into areas where mosquito-borne disease is prevalent can avoid unnecessary exposure by locating camp sites at distances from breeding places and native habitations that are greater than the flight range of the vector, due regard being taken of the direction of prevailing winds.<sup>140, 141</sup>

Numerous substances have been used as repellents; they are at best transitory, and some are toxic if used liberally. At present there are three fairly good repellents—"612," Indalone and dimethyl phthalate.<sup>142</sup> The first gives protection for about four hours, even when persons are sweating. Indalone lasts equally long except under sweating conditions, when it should be reapplied every half



War I, since lousiness was characteristic of all troops. The present war, however, has brought about miraculous developments in delousing techniques,<sup>161</sup> resulting in virtual elimination of epidemic typhus from the Army and its control among civilians in combat areas. Methyl bromide fumigant in cartridges is available for disinfecting clothing in barrack bags. More phenomenal in its success against the head and body lice (*Pediculus humanus capitis* and *P. humanus corporis*) has been the application of D. D. T. powder to both the body and clothing. These drugs are also effective against fleas but have no effect against mites.

Endemic or murine typhus is spread by fleas. About 90 per cent of the 4000 cases reported annually in the United States occur in Alabama, Texas and Georgia.<sup>162</sup> In 1926, Maxcy<sup>163</sup> made important epidemiologic studies, which eliminated the possibility of louse transmission of typhus fever in southern United States. In 1931, Dyer and his associates<sup>164</sup> obtained murine typhus from the brains of rats captured in a prison in Mexico City. It has since been demonstrated that the infection is passed from rat to rat by both rat fleas (*Xenopsylla cheopis*) and rat lice (*Polyplax spinulosa*).

Scrub typhus or tsutsugamushi fever is transmitted by several species of Trombicula mites and does not occur in the United States.<sup>165, 166</sup> It is prevalent in the South Pacific and Asia. Clothing impregnated with dimethyl phthalate is efficient in killing the mite vectors.<sup>167</sup> The burning over of areas used to bivouac troops is effective in ridding the area not only of fleas and mites but also rodents and other vermin that may act as vectors of disease.

These three types of typhus fever are immunologically distinct<sup>168</sup> and can be identified in the laboratory by Weil-Felix reaction and by complement-fixation tests.<sup>169</sup> Vaccines have been prepared by various methods,<sup>170</sup> employing chick embryos, lice and so forth, and have proved effective against the epidemic and endemic forms of the disease. The same vaccine, however, is not effective against scrub typhus.

Rodent control is, of course, of importance in the control of endemic typhus fever,<sup>171</sup> but the control of rodents in other rickettsial diseases is only of value under limited circumstances. Nevertheless, wild rodents, from field mice to rabbits, may be hosts of the exoparasites that are infected with various types of rickettsia.<sup>172</sup>

#### DICHLORO-DIPHENYL-TRICHLOROETHANE

D. D. T. was first synthesized by a German chemist in 1874,<sup>173</sup> but it was not used as an insecticide until 1939, when a Swiss firm sold it as a control for moths and plant lice. Since November, 1942, the United States Department of Agriculture has experimented with D. D. T., not only as a control for agriculture insect pests but as a control for arthropod vectors.

D. D. T. is a tasteless, fine, white powder, insoluble in water. It tends to form lumps, is not affected by exposure to the air and sunlight and does not vaporize. The residue on a sprayed surface retains its toxicity as a contact poison to insects for several weeks.<sup>61</sup> It is easily dispersed in dust and forms an emulsion with oils.

A powerful poison to the insect nervous system, it is absorbed through the chemotactic sensory organs in the tips of tarsi. Soon after exposure, the insect drags its legs, loses co-ordination, develops tremors and dies in convulsions. It is not a repellent and does not kill instantaneously like pyrethrum; death usually takes from several minutes to several hours.

Although the dry powder is not absorbed through the skin, concentrated oily emulsions are absorbed and may prove toxic in large doses, causing hyperexcitability, tremors, chronic convulsions and liver damage.<sup>174</sup> Precautions must therefore be taken to avoid repeated and prolonged contact with oil emulsions. Inhalations of heavy concentrations of D. D. T. smokes have not proved toxic to either animals or man. When ingested, however, D. D. T. is toxic for both animals and man, 200 mg. per kilogram of body weight per day killing 90 per cent of the test animals. When applied to water in the amounts recommended for larvicidal purposes, it is not toxic to fish, animals or man. Cyclohexanone is frequently used as a solvent for D. D. T.; although it is less than one tenth as toxic as D. D. T., in heavy concentrations it causes a temporary, harmless irritation of the eyes, nose and lungs.

D. D. T. may be mixed with 9 parts of inert powder for use as an insecticide or with the same amount of talc or pyrophyllite for use against body lice. An emulsion containing 25 per cent D. D. T., 68 per cent xylene and 7 per cent Tritonx-100 may be diluted with 4 parts of water, making a 5 per cent emulsion; or the pure powder may be mixed with No. 2 fuel oil, No. 10 lubricating oil, kerosene or other oils to form a 5 per cent emulsion. Aerosol bombs containing 0.3 per cent pyrethrins and 3 per cent D. D. T. have been demonstrated to be effective as an all-purpose insecticide. Such bombs should prove of value in disinsectizing planes. Special nozzles for spraying or dusting equipment are required, depending on the use to which the drug is being put. A fog is most effective against adult insects; for larvicidal purposes a fine spray is best; and for a residual effect on solid surfaces a coarse or semi-fine spray is needed to moisten the surface. A residual of 0.1 to 0.2 gm. of D. D. T. per square foot is desired; thus 1 liter of a 5 per cent solution is adequate for 250 to 500 square feet. The drug continues to be effective for weeks or months, depending on climatologic conditions. The drug may be sprayed both indoors and out. Although D. D. T. tends to stick to surfaces, heavy rains wash off a considerable amount, which may be detectable in the runoff.

abundant colonies of *Staphylococcus aureus*. Repeated serum nonprotein nitrogen and carbon dioxide determinations were normal. The sulfadiazine level did not exceed 6 mg. per 100 cc. The white-cell count and the differential were unchanged. The patient was given 50,000 units of penicillin and was placed in an oxygen tent. A surgical consultant thought that the abdomen and the subphrenic region were negative. On the sixth day, the patient felt much better and the rectal temperature had fallen to 100°F. At 3

On the second hospital day the chest was somewhat better aerated and the respiratory rate returned to 20. The gall bladder was faintly visualized in a Graham test.

On the fourth day a definite gallop rhythm was heard at the apex. Fresh blood was seen in the sputum. There was a definite but mild cellulitis of the left forearm. Measurements above and below the knees were symmetrical. The rectal temperature



Figure 1.

reached 103°F., and sulfadiazine was started. The pulse fluctuated between 100 and 120, and the respirations between 25 and 35. A thoracentesis in the ninth interspace on the right posteriorly yielded 60 cc. of grossly bloody fluid containing 6000 lymphocytes and monocytes per cubic millimeter. After the chest tap the respiratory rate was elevated to 60. Localized edema was noted over the painful area in the right chest posteriorly. There was tenderness in the costovertebral angle. A catheterized specimen of urine showed occasional red cells and 75 white cells per high-power field, and rare coarsely granular casts. A smear of the sediment showed a moderate number of gram-positive cocci in clusters, and a culture yielded

Dr. DEKA KINSEY: Out of this long and complicated story we have little definite knowledge. We do know, however, that this sixty-four-year-old patient had been chronically ailing for at least one year. His chief complaints were chest pain, weight loss, abdominal pain and urinary difficulties. The final illness came on suddenly; it may have been a part of the chronic illness or something new.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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#### CASE 31131

##### PRESENTATION OF CASE

A sixty-four-year-old man was admitted to the hospital because of hemoptysis and abdominal pain.

He had been in good health until approximately a year before admission, when he first noted a dull, aching, nonradiating, intermittent pain under the lowest rib in the right midaxillary line. Six weeks before entry he became aware of a gradual weight loss, amounting to about 16 pounds in the previous six months. He also began to notice mild anorexia and malaise. Urgency, frequency and dribbling, which had been present for two years, became more intense. Three weeks before admission and five to six hours after ingesting a heavy meal, he was suddenly awakened at night by a severe, constant, periumbilical pain, which radiated to the perineum and to the tip of the xiphoid. So intense was this pain that he vomited and spent the next five hours in agony. He worked the next day, although the pain was still present. It persisted throughout the following week and he was taken to a community hospital. He continued to be nauseated and the abdominal pain shifted from the periumbilical region to the right upper quadrant, where it localized. He remained afebrile. His stool habits and the gross appearance of the stools remained normal. Cystoscopy, a gastrointestinal series and a barium enema were reported as negative. A retrograde pyelogram was negative except for questionable blunting of the middle calyces on the right. An intravenous pyelogram showed no visualization of the right kidney. X-ray studies of the chest were reported to show bilateral basal atelectasis and

diminished excursion. During the four days before entry the pain in the right upper quadrant continued intermittently. He developed a cough, with small hemoptyses, and was transferred to this hospital.

Except for dysuria, nocturia (twice) and frequency the past history was noncontributory.

Physical examination revealed a well-developed, moderately well-nourished man in no acute discomfort. Examination of the heart was negative. The breath sounds were diminished at the right base posterolaterally and as far forward as the anterior axillary line. Over this same area there were fine rales and dullness to percussion. Localized pain with respiration and a friction rub were noted over the left lower chest posterolaterally. The abdomen and extremities were normal.

The temperature was 99.2°F., the pulse 100, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

The urine was acid, with a specific gravity of 1.017, and gave a + test for albumin; the sediment contained numerous white cells and bacteria. Examination of the blood showed a white-cell count of 11,100, with 92 per cent neutrophils, and 10.5 gm. of hemoglobin. The serum nonprotein nitrogen, the protein and the chloride were normal.

X-ray studies of the chest revealed retarded motion of both leaves of the diaphragm, the right more than the left. Above them, linear areas of atelectasis were observed at each base, and on the right there were also patchy areas of increased density. It was thought that a small amount of fluid might be present in the right pleural sinus (Fig. 1). There was little change since the last x-ray taken in the other hospital, three days prior to admission.

During the patient's first night in the hospital the pain in the right posterior chest was severe and aggravated by cough. The pain was readily localized to an area under and to the right of the angle of the right scapula. Inspiration was limited, and the respiratory rate was 35. The rectal temperature was 101°F., and the pulse 110. The abdomen was distended, tympanitic and tense. There was questionable tenderness in the right upper quadrant. The calves were not tender, and there was no tenderness over the femoral veins. The patient raised a small amount of blood-streaked sputum. Repeated examinations and cultures of the sputum were nega-

\*On leave of absence.

cellulitis of the forearm, which might have been the focus. I believe that he also had an acute infectious process, such as a bacterial endocarditis or a bronchopneumonia.

Dr. CHESTER M. JONES: This case was confusing because from the moment the patient entered the hospital the suggestion was made that he had a subphrenic abscess. That was as near as anyone had approached the diagnosis before he entered the hospital. The striking fact on admission was the clinical picture. He was extremely ill. He was badly distended and had been vomiting. He had a story that was difficult to obtain, but it pointed to an intrabdominal disturbance, so far as we could find out. He remained extremely distended for several days, and then the distention disappeared after an enema and did not recur. I suppose the distention caused the elevation of the diaphragm.

He continued to complain of abdominal pain, but my feeling, in view of the x-ray studies that had been taken prior to admission, was that intratestinal disease had been ruled out and that renal disease probably had been ruled out. I wondered whether or not he had an empyema of the gall bladder with perforation. He was tender in the right upper quadrant, but it was also apparent that he had abundant physical signs, including a friction rub, first in the left chest and later in the right. He had pain over the area of pulmonary signs; in other words, he had pain in the chest over the friction rub. I went over the previous chest films and the ones taken here and discussed them with several members of the x-ray staff. There was no final conclusion concerning what was going on above the diaphragm.

Chemotherapy was started because of a marked rise in temperature. At that time he had a striking cellulitis of the left arm that seemed to be associated with intravenous therapy, initiated because of severe dehydration. The following day he was seen by Dr. Sweet to determine if possible what was going on in the chest and to decide whether or not he had a subdiaphragmatic infectious process. By that time the fever had subsided, although the patient was still extremely sick. We went over his legs with the utmost care, because the question of pulmonary embolism had been raised, but we could not find any evidence of a thrombotic process. There was no tenderness, and he had a negative Homans's sign. The white-cell count was about 11,000, and at that time we tapped the right chest, inasmuch as the physical signs seemed more striking than the x-ray findings. We found bloody fluid. This was spun down and examined for malignant cells, without result. Furthermore, several specimens of sputum were examined for tubercle bacilli and the chest fluid was put into a guinea pig, also with negative results. Until the last episode we were definitely in doubt about what the patient had. I thought that he had intrabronchopneumonia.

Clinical Diagnoses  
Pulmonary embolism.  
Intra-abdominal infection of undetermined nature?  
Dr. KINSEY'S DIAGNOSES  
Renal-cell tumor of right kidney, with thrombophlebitis of renal vein and metastases to lung.  
Terminal infection: (?) bronchopneumonia or bacterial endocarditis.  
Anatomical Diagnoses  
Pulmonary embolism, massive.  
Pulmonary infarcts: multiple, bilateral, recent and healing.  
Phlebotrombosis of leg veins.  
Pathological Discussion  
Dr. BENJAMIN CASTLEMAN: The autopsy showed that the terminal event was a massive pulmonary embolus and that most of the previous symptoms were probably due to smaller pulmonary emboli. At the edge and margin of the anterior surface and posteriorly along the diaphragm were numerous infarcts, which extended up to involve about the lower third of each lung. In several areas they were quite thin because they extended to the edge and had contracted down a bit. Some of them, especially one in the left lung, had a dimple on the pleura indicating that this was a healing infarct and could have been there for a matter of a month or two. Others were more recent. In other words, they varied in age from a couple of months down to a week or ten days. Some were red, and others were black and rather well circumscribed, with beginning encapsulation. The calf veins of both legs were the source of the emboli.

The kidneys were perhaps slightly larger in size than normal and showed evidence of pyelitis, which was apparently the source of the *Staphylococcus aureus*. We were unable to find any infection in the parenchyma of the kidney itself. One microscopic section showed a thrombus in a small vein, and a small focus of tissue nearby was infarcted. There were no large thrombi or emboli. I am sure that this was not the cause of the severe abdominal pain; if so, there would certainly have been a larger infarct. Perhaps all his pain was referred from the pulmonary infarcts. He had them in both lower lobes, and there was an extensive diaphragmatic pleuritis.

Dr. JONES: The original pain that sent him into the hospital was in the lower abdomen. That was the one point that he stuck to all the time. It brings out the point that pain arising from the attachment

Had this man one disease process to explain all his symptoms or had he more than one? First let us consider the chest. He had had chest pain for one year and more acute pain recently. Pneumonia occasionally causes acute abdominal pain and sometimes is mistaken for an acute abdomen. The x-ray findings, the white-cell count and the temperature, however, are not in keeping with it. The x-ray examination also rules out tuberculosis. Furthermore, tuberculosis usually does not give a bloody pleural fluid. On the other hand, the bloody fluid, the weight loss and the age of the patient should make one consider metastatic malignancy. A likelier possibility is pulmonary infarction. The chest pain, the cough and the raising of blood-tinged sputum are classic symptoms. Infarctions are usually secondary to thrombophlebitis or thrombosis in the lower extremities. The emboli may originate, however, in any of the large veins or in the right side of the heart itself. The physician who took care of this patient evidently suspected pulmonary infarction because a careful search was made for the focus of the emboli but apparently none was found. Another suggestion of pulmonary infarction is the development of gallop rhythm. An electrocardiogram might have been helpful.

The patient's most acute symptom was abdominal pain, which began in the periumbilical region and radiated to the perineum and to the xiphoid. Frequent causes of periumbilical pain are small-bowel obstruction, — which may be caused by a malignant tumor, — kink, hernia and intussusception. All these things seem to be ruled out because the patient had normal stools, all the x-ray examinations were negative, and the vomiting ceased. The type of pain does not suggest disease of the gall bladder or acute pancreatitis. Cardiac decompensation with a large engorged liver can certainly cause severe abdominal pain of the type described here. We have no evidence, however, that the liver was large and engorged, and the only suggestion of congestive failure was the gallop rhythm. A subphrenic abscess with rupture into the pleural cavity may cause a combination of abdominal and chest pain. The character of the chest fluid and the absence of chills and of a high white-cell count are against this diagnosis. A dissecting aortic aneurysm can also produce abdominal and chest pain. The pain of a dissecting aneurysm, however, usually radiates to the back and down the legs.

May we see the x-ray films?

DR. MILFORD D. SCHULZ: Here is a series of films of the chest. At the time of the original observation, the fluoroscopist saw nothing in the chest. In the film taken ten days later, however, the findings are as described — linear areas of increased density obscuring both leaves of the diaphragm and elevation of the leaves of the diaphragm. These changes persisted throughout the subsequent ob-

servations. This film, after retrograde filling of the right kidney, shows irregularity of the middle calyx. I wonder if it is not the filling that one sees in a retrograde pyelogram that has caused overdistention of the pelvis. All the calyces are blunted. The kidney appears to be normal. I should think it was probably all right.

These are the films of the intravenous pyelogram; unfortunately they do not show much. Because of barium in the colon, the visualization is not too adequate, but you can see fairly distinct calyces and no evidence of obstruction on either side.

DR. KINSEY: Then you can see the right kidney?

DR. SCHULZ: The kidney outline is obscured by overlying material.

DR. KINSEY: You cannot see the calyces?

DR. SCHULZ: I believe that you can in this film. There is a faint shadow that probably represents the pelvis and some of the calyces, but it is not good enough to warrant any statement.

DR. KINSEY: An intravenous pyelogram showed no function of the right kidney but the retrograde pyelogram showed a practically normal kidney, with the exception of blunting of the middle calyces. This indicates or suggests that something was interfering with the blood supply of that kidney. What might interfere with the blood supply? Thrombosis of the renal artery with infarction is a possibility and would have caused pain. It might even have been a thrombosis of the renal veins. A tumor such as a renal-cell carcinoma might explain many of the symptoms and signs, although the three most frequent findings — tumor, hematuria and pain referable to the kidney area — are absent. Renal-cell carcinoma or hypernephroma is very apt to extend up the renal vein into the inferior vena cava and to metastasize to the lungs, and in one case report of this condition from this hospital the outstanding symptoms were gastrointestinal.

Then I thought of one other possibility — subacute bacterial endocarditis of long duration, with mural thrombi giving out infected emboli and causing infarction in various parts of the body. This patient, however, had no evidence of rheumatic valvular lesions, which are usually present in subacute bacterial endocarditis. In fact, not many heart symptoms were noted. It seems that there was an additional terminal infection; those who took care of him probably thought that, because they gave sulfadiazine and penicillin.

In reading the abstract I made the following diagnoses and I shall stick to them even though they do not seem quite so obvious after looking at the x-ray films: tumor of the right kidney, probably renal-cell tumor, with thrombophlebitis of the renal veins and with metastases to the lungs; and pulmonary infarcts, which may or may not be associated with the thrombophlebitis of the renal veins, because we do know that silent emboli may come from the extremities. We were told that he had a



to make our way into this, it soon became apparent that whatever tumor was here had invaded the duodenum directly. The gall bladder and bile ducts formed a solid tumor mass, which was biopsied. We could not identify any portion of normal duct above the tumor mass that could be used for anastomosis. Because of the fact that the duodenum was partially destroyed by the tumor mass, a resection of the distal end of the stomach and the first portion of the duodenum had to be performed. Even this much surgery in the face of a complete and unrelieved biliary obstruction was doomed to terminate fatally. About ten days after the operation, the patient slipped into coma and died quietly, a death that I should characterize as being typical of liver failure or cholemia.

#### CLINICAL DIAGNOSIS

Cholelithiasis, with common-duct stone.

DR. DONALDSON'S DIAGNOSIS

Cholelithiasis, with common-duct stone.  
Chronic cholecystitis.

Bile stasis of liver.

#### ANATOMICAL DIAGNOSIS

Colloid carcinoma of gall bladder, with extension to extrahepatic bile ducts and metastases to head of pancreas and regional lymph nodes.

Cholelithiasis.

Bile stasis of liver.

#### PATHOLOGICAL DISCUSSION

DR. SYFFER: When he died the patient was deeply jaundiced. Dr. Moore had resected the distal end of the stomach and proximal portion of the duodenum. This was followed by a gastrojejunostomy and infolding of the duodenal stump. All suture lines were intact, but the proximal end of the duodenum lay in a necrotic mass of fibrinopurulent adhesions. The gall bladder was destroyed by a tumor that was fixed to the surrounding viscera by fibrous adhesions, and its necrotic center contained a 3-by-2-cm. gallstone. The tumor had spread to the cystic and common bile ducts and to both hepatic ducts, leading to complete obliteration of their lumens. The adjacent liver parenchyma was also invaded. The whole mass measured approximately 6 by 4 cm. The head of the pancreas contained a few minute, discrete metastatic nodules. Microscopic sections showed a colloid carcinoma. The liver was large, weighing 1990 gm., and its surface was smooth and dark green. The intrahepatic bile ducts were distended with bile. Microscopic sections showed a rather severe bile stasis without other abnormalities except for degeneration in the neighborhood of the invading tumor.

have been others. These patients were mildly jaundiced and then cleared, only to become icteric again one or two months later. The mechanism of this is hard to explain, but it does occur. Local edema, the rate of bile flow and the type of bile have been offered as explanations. Here again, however, if the obstruction were this far down the biliary tree one would expect gall-bladder distention. Cancer of the gall bladder or upper biliary tree is in the same order of likelihood. In such conditions the patient should be a little less robust than the report leads one to suspect. Primary cholangitis of the stenosing type is unlikely in the absence of chills and fever. Similarly, biliary obstruction from an ascending pyelephlebitis has no historical or clinical support. I shall have to conclude that the operator on opening the abdomen expected to find a slightly enlarged heavily pigmented liver, a thickened, shrunken gall bladder and a somewhat dilated and edematous common duct. A stone had been passed fifteen months before. Another was probably lodged in the common duct, and more lay in the gall bladder. The epigastric soreness and tenderness were due to this stone. The dark black stools noted on several occasions two weeks before entry probably resulted from erosion by a stone of one of the veins that are so abundant in the common-duct wall. A fistula may have existed between the gall bladder and common duct, but this is unlikely. A prothrombin time, prolonged by obstructive liver damage, prevented early clotting and resulted in the degree of anemia found. Further evidence of the degree of liver damage is found in the lowered albumin-globulin ratio and in the elevated van den Bergh reaction.

DR. ROYALD C. SYFFER: Dr. Moore, you operated on this case. Will you tell us about your findings? DR. FRANCIS D. MOORE: An item that might have helped Dr. Donaldson is the fact that the black stools occurred while he was in an outside hospital and while he was receiving iron therapy. They were not guaiac or benzidine positive, and so far as we can make out, he had never had any proved evidence of gastrointestinal bleeding. This is important because gastrointestinal bleeding in cases of common-duct stone is extremely rare, even in the presence of a markedly elevated prothrombin time.

In any event, we expected to find approximately what Dr. Donaldson has described, namely, the changes caused by chronic cholecystitis and cholelithiasis, with a common-duct stone. The situation was quite different, however, from what we expected. The duodenum, large intestine, stomach, pancreas, gall bladder and common duct were all drawn up into the liver hilus, where they were firmly matted together by an extensive neoplastic and inflammatory process. In attempting

of the diaphragm can spread over the distribution of the twelfth intercostal nerve. Another point of which I was not aware is that one can occasionally obtain bloody fluid from the pleural cavity in cases of pulmonary infarction.

DR. CASTLEMAN: I should say that 10 or 15 per cent of pulmonary infarcts have associated hemorrhagic pleural fluid.

X-ray examination of the abdomen showed no opaque calculi along the course of the renal or biliary tracts. The lumbar spine was not unusual, and the psoas contours were normal. There was no enlargement of the liver or spleen. The right kidney was thought to be somewhat enlarged.

On the fifth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. GORDON DONALDSON: In the absence of the x-ray films, we will have to content ourselves with the written report. On x-ray examination, the liver was not enlarged and no evidence of gallstones was seen. The enlargement of the right kidney can be interpreted as being within the limits of normal.

I think that this man had either cancer or calculi obstructing the outflow of bile from the liver, with the odds heavily in favor of stone. A portal or toxic type of cirrhosis seems unlikely in view of his pain, short story, lack of ascites and general well-being. Moreover, a jaundice of the catarrhal type is reasonably well ruled out by the story and physical findings. Catarrhal jaundice does not recur, particularly after a fourteen-month interval.

The jaundice was obstructive in nature and was of the type that was not accompanied with bouts of chills and fever. The pain, moreover, was probably due to whatever caused the obstruction, and not to the liver itself, since a distention of the liver capsule sufficient to cause pain should result in a palpable liver or one seen to be enlarged by x-ray. From the location of the pain one might suspect a gastric or duodenal ulcer, with secondary distortion and constriction of the common duct. Such deforming ulcers, however, are usually of much longer duration and are found in much sicker patients. An obstructing duodenal diverticulum should be mentioned in passing. Obstructing disease in the pancreas is a possibility, but if present, the location and type of pain are unusual. Patients with cancer of the head or body of the pancreas usually have pain in the midback. Cyst of the pancreas is rare but can cause obstruction. Certainly if the obstruction to the flow of bile is strictly pancreatic in origin, one should be able to feel the distended gall bladder on abdominal examination.

Carcinoma of the ampulla of Vater should be given consideration. To be sure, such a lesion rarely causes pain, and when it does it is not in the mid-epigastrium. Bleeding, however, is a fairly common finding; and in this patient we have a history of black stools and the report of a moderately severe anemia. It is only fair to say that the fecal blood in carcinoma of the ampulla is usually occult. A history of definite jaundice that fades out only to recur does not rule out carcinoma of the ampulla. Such a case was reported here not long ago,\* and there

\*Case records of the Massachusetts General Hospital (Case 30381). *New Eng. J. Med.* 231:427-429, 1944.

### CASE 31132

#### PRESENTATION OF CASE

A fifty-three-year-old man was admitted to the hospital because of deep jaundice.

He had been well until fifteen months before entry, when he suffered an acute onset of dull epigastric pain. At about the same time he noticed the appearance of moderate jaundice, dark urine and light-colored stools. A physician gave him "some pills" and the jaundice allegedly disappeared, having been present only about fifteen to twenty hours. The epigastric pain and a feeling of fatigue, however, lasted several days longer.

Following this episode he was well until about five weeks before admission, when a steady epigastric pain recurred and was associated with occasional nausea and vomiting of liquid material that resembled "olive oil." Three weeks before admission he rapidly developed marked jaundice, with dark urine and light-colored stools. The epigastrium was a little "sore" and slightly tender. The degree of jaundice had fluctuated slightly and there were a few bouts of nausea and vomiting. He had no fever, chills or colicky or radiating pains. He stated that he had had black stools for several days about two weeks before admission.

Physical examination revealed a well-developed, well-nourished man in no distress. The skin and scleras were deeply jaundiced. The heart and lungs were not remarkable. The abdomen was not distended and showed no mass or tenderness.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 65 diastolic.

Examination of the blood showed a red-cell count of 3,690,000, with 10.9 gm. of hemoglobin, and a white-cell count of 11,600, with 85 per cent neutrophils. The urine was dark, acid in reaction and had a specific gravity of 1.012. It gave a + test for albumin and a +++ test for bilè. The sediment contained a few granular casts. A van den Bergh test was 23.5 mg. per 100 cc. direct, and 32.4 mg. indirect. The stool was olive green and guaiac negative. The prothrombin time was 27 seconds (normal, 18 to 20 sec.). The serum nonprotein nitrogen and total protein were normal, with an albumin-globulin ratio of 1.04.

to make our way into this, it soon became apparent that whatever tumor was here had invaded the duodenum directly. The gall bladder and bile ducts formed a solid tumor mass, which was biopsied. We could not identify any portion of normal duct above the tumor mass that could be used for anastomosis. Because of the fact that the duodenum was partially destroyed by the tumor mass, a resection of the distal end of the stomach and the first portion of the duodenum had to be performed. Even this much surgery in the face of a complete and unrelieved biliary obstruction was doomed to terminate fatally. About ten days after the operation, the patient slipped into coma and died quietly, a death that I should characterize as being typical of liver failure or cholemia.

#### CLINICAL DIAGNOSIS

Cholelithiasis, with common-duct stone.

DR. DONALDSON'S DIAGNOSIS

Cholelithiasis, with common-duct stone.  
Chronic cholecystitis.

Bile stasis of liver.

#### ANATOMICAL DIAGNOSIS

Colloid carcinoma of gall bladder, with extension to extrahepatic bile ducts and metastases to head of pancreas and regional lymph nodes.

Cholelithiasis.

Bile stasis of liver.

#### PATHOLOGICAL DISCUSSION

DR. SNIFFEN: When he died the patient was deeply jaundiced. Dr. Moore had resected the distal end of the stomach and proximal portion of the duodenum. This was followed by a gastrojejunostomy and infolding of the duodenal stump. All suture lines were intact, but the proximal end of the duodenum lay in a necrotic mass of fibrinopurulent adhesions. The gall bladder was destroyed by a tumor that was fixed to the surrounding viscera by fibrous adhesions, and its necrotic center contained a 3-by-2-cm. gallstone. The tumor had spread to the cystic and common bile ducts and to both hepatic ducts, leading to complete obliteration of their lumens. The adjacent liver parenchyma was also invaded. The whole mass measured approximately 6 by 4 cm. The head of the pancreas contained a few minute, discrete metastatic nodules. Microscopic sections showed a colloid carcinoma. The liver was large, weighing 1990 gm., and its surface was smooth and dark green. The intrahepatic bile ducts were distended with bile. Microscopic sections showed a rather severe bile stasis without other abnormalities except for degeneration in the neighborhood of the invading tumor.

one would expect gall-bladder distention. Cancer of the gall bladder or upper biliary tree is in the same order of likelihood. In such conditions the patient should be a little less robust than the report leads one to suspect. Primary cholangitis of the stenosing type is unlikely in the absence of chills and fever. Similarly, biliary obstruction from an ascending pyelophlebitis has no historical or clinical support.

I shall have to conclude that the operator on opening the abdomen expected to find a slightly enlarged, heavily pigmented liver, a thickened, shrunken gall bladder and a somewhat dilated and edematous common duct. A stone had been passed fifteen months before. Another was probably lodged in the common duct, and more lay in the gall bladder. The epigastric soreness and tenderness were due to this stone. The dark black stools noted on several occasions two weeks before entry probably resulted from erosion by a stone of one of the veins that are so abundant in the common-duct wall. A fistula may have existed between the gall bladder and common duct, but this is unlikely. A prothrombin time prolonged by obstructive liver damage, prevented early clotting and resulted in the degree of anemia found. Further evidence of the degree of liver damage is found in the lowered albumin-globulin ratio and in the elevated van den Bergh reaction.

DR. DONALD C. SNIFFEN: Dr. Moore, you operated on this case. Will you tell us about your findings?

DR. FRANCIS D. MOORE: An item that might have helped Dr. Donaldson is the fact that the black stools occurred while he was in an outside hospital and while he was receiving iron therapy. They were not guaiac or benzidine positive, and so far as we can make out, he had never had any proved evidence of gastrointestinal bleeding. This is important because gastrointestinal bleeding in cases of common-duct stone is extremely rare, even in the presence of a markedly elevated prothrombin time.

In any event, we expected to find approximately what Dr. Donaldson has described, namely, the changes caused by chronic cholecystitis and cholelithiasis, with a common-duct stone. The situation was quite different, however, from what we expected. The duodenum, large intestine, stomach, pancreas, gall bladder and common duct were all drawn up into the liver hilus, where they were firmly matted together by an extensive neoplastic and inflammatory process. In attempting

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## SURGERY OVER THERE

THE September issue of the *Annals of Surgery* contains a paper by Colonel Edward D. Churchill, who is on leave from the Massachusetts General Hospital while serving as surgical consultant to the North African and Mediterranean Theater of Operations. This paper has been characterized by Brigadier General Rankin as "one of the finest dissertations on the management of wounds which has been submitted through the Office of The Surgeon General of the United States Army." In a foreword to this article General Rankin writes:

Colonel Churchill has done more than improve the quality of surgery performed in this theater. Uniquely equipped to perform his mission and imbued with the true scientific spirit, he early recognized the inadequacy

of certain preformed concepts in the surgical management of the wounded. With this flexibility of mind and with an elastic organization, he has utilized an investigative approach and drawn upon battlefield experience to evolve more rational and effective methods in the surgical care of the wounded. In this article, he has epitomized these observations and principles which constitute not only a contribution to war surgery but also to the advancement of medical science.

Every surgeon interested in the management of traumatic wounds should read this brief paper in the original. Others will get a great deal of satisfaction from reading it and learning of the methods now being employed in the management of severe battle injuries. Dr. Churchill dispels a number of important misconceptions, particularly concerning the role of blood substitutes and of chemotherapeutic agents, including penicillin, in the management of wounds and indicates the greater importance of prompt and adequate surgical treatment. No better comment on this paper could be made than to quote a few excerpts\* that are as applicable to traumatic surgery in civilian life as they are to the management of injuries sustained on the battlefield:

... Plasma alone is not adequate to prepare a seriously wounded casualty to withstand the surgical procedures that are essential, or to carry him through the critical postoperative period. After admission to hospital a limited amount is used to augment the effects of whole blood transfusion. Plasma is a substitute for whole blood only in the sense that it can be packaged and stored in adequate quantity in areas where blood cannot be obtained. Plasma is not a substitute for whole blood in the physiologic sense. . . .

Chemotherapy is initiated in the field by local and oral administration of sulfonamides. The value of this procedure is questioned by many surgeons of experience. Preoperative penicillin therapy is started on all but the lightly wounded casualties on admission to hospitals in the forward area. At operation, topical application of penicillin is carried out only in wounds penetrating the meninges, serous cavities and joints. Parenteral administration is continued beyond the period of the likelihood of infection or until established infection has been controlled. No patient is held in the forward area solely for the purpose of continuing penicillin therapy.

Just as plasma is not a substitute for whole blood in resuscitation, neither are sulfonamides and penicillin substitutes for the surgical excision of devitalized tissue. Chemotherapeutic agents cannot sterilize dead, devitalized or avascular tissue, nor do they prevent the septic decomposition of contaminated blood clot. . . .

In this war there have been two quite different approaches in the application of chemotherapeutic agents to military surgery. The first would utilize these agents to permit delay in wound surgery and minimize the complete-

\*Permission to quote these excerpts has been obtained from the copyright owner, J. B. Lippincott Company, Philadelphia

ness of the excision of dead tissue. The second employs chemotherapeutic to extend the scope of surgery and achieve a perfection in results previously considered impossible. The latter policy has guided the surgery of the Alcler-ranean Theater. To reiterate the axiom that penicillin is not a substitute for surgery is not enough. Every surgeon must learn that chemotherapy opens new and startling possibilities in wound management. . . .

Surgeons assigned the responsibility of caring for the wounded in a first priority surgical hospital must be highly trained and experienced, as their tasks are the most exacting of military surgery. . . . If the achievements of surgery in this theater are ever judged noteworthy, they are attributable to the fact that experts rather than inexperienced surgeons are doing the work. All other measures are ancillary items. . . .

It is estimated that during the Italian Campaign alone at least 25,000 soft-part wounds have been closed on the basis of gross appearance only. Healing has resulted in approximately 95 per cent, and no loss of life or limb or serious complications have been reported. . . . The presence of residual dead tissue or established invasive infection at the time of the first dressing is evidenced by discharge of pus and redness and edema of the wound margins. When these are present but minimal, the wound is allowed to "clean up" with moist dressings. Surgical excision of devitalized fragments or removal of retained foreign bodies may speed this process. Secondary closure may then be performed after a few days. If established infection is severe, or if the patient is toxic or anemic, a course of penicillin therapy and blood transfusions is instituted and followed by radical wound revision with staged closure. . . .

The topical use of sulfonamides appears to contribute nothing to the favorable results of reparative wound surgery. Partial series of closures show as satisfactory or better results without the topical application of sulfonamides at the time of suture as with it. Penicillin therapy is entirely unnecessary as an adjunct to the usual reparative surgery of soft-part wounds. It is used parenterally for cases of established infection and in the reparative surgery of complicated wounds. . . .

The reparative surgery of complicated wounds, including those with extensive muscle damage as well as those with skeletal or joint injury and penetration of the viscera, is a more major undertaking. It is in this group that both the incidence and hazards of infection may be expected to be greater. It is this group of cases that is kept on penicillin therapy during the interval between initial and reparative surgery and so maintained until the likelihood of infection is past. Immediate correction of secondary anemia on arrival at the base is an essential part of the program as the days are few during which the anemia from the initial blood loss may be projected into the anemia of chronic infection and indolent wound healing. The procedures of reparative surgery are frequently of great magnitude and the patients must be adequately supported by whole-blood transfusions, before, during, and subsequent to operation. . . .

The time-lag between wounding and initial surgery referred to as "the golden period" has been greatly reduced by the organization of medical service in the forward area to this end. The time-lag between initial surgery and reparative surgery is now assumed an equal degree of importance. Just as every hour added to the time-lag between injury and initial surgery increases the loss of life and limb, so does every day added to the time-lag between initial and reparative surgery. Four to ten days is "the golden period" to close wounds, reduce and fix fractures, remove retained missiles and carry out other procedures to prevent or abort infection. To fail to take cognizance of the potentialities of early reparative surgery at the base in the future plans and operations will be as unthinkable as a failure to plan for the removal of the wounded from the field of battle. . . .

It is a satisfaction to note the contrast between the present concept of wound management and the doctrines in vogue scarcely a year ago. The closed-plaster management of wounds and fractures was designed to conserve life but exacted a high price in skeletal and soft-part deformity. Its use is now limited to certain cases with established infection of bone or with massive defects of soft parts compounding a fracture site. Recommendations that minimized the necessity for a complete initial wound operation or sought to delay it (wound trimming, "salting down with sulfa drugs" and so forth) accepted supputation as inevitable in a considerable proportion of cases and relied on chemotherapy to hold sepsis within bounds. Resuscitation measures that relied on plasma alone to compensate for loss of whole blood prolonged life but tied the hands of the surgeon in the performance of life-saving surgery. These and other earlier concepts were but faltering steps toward what will emerge as the ultimate scope of surgery as developed in the present war.

## MASSACHUSETTS MEDICAL SOCIETY SECRETARY'S OFFICE

The following communication concerning cancellation of the annual meeting of the Massachusetts Medical Society has been sent to the Executive Committee of the Council:

Dear Doctor:

The Office of Defense Transportation has denied our petition to hold the annual meeting of the Massachusetts Medical Society. This applies equally to the annual meeting of the

These events will, therefore, not be held in 1945. Dr. Elmer S. Bagnall, President, has ruled that the carrying on of our Society's affairs during this emergency is the obligation of the Executive Committee of the Council.

The next meeting of the Executive Committee has been set for 10:30 a.m., Wednesday, May 23, 1945, at Sprague Hall, 8 Fenway, Boston. The agenda of this meeting will be sent to each councilor well in advance.

On its receipt the president of each District Medical Society should call the councilors of his district together for the purpose of studying it and making determinations with

regard to it, to the end that the executive councilor may come to the meeting in May aware of and fully prepared to express his district's point of view.

The Cotting Luncheon will be served.

Very truly yours,

Michael A. Tighe, *Secretary*

## DEATHS

**BERGIN** — Stephen A. Bergin, M.D., of Worcester, died February 22. He was in his seventy-second year.

Dr. Bergin received his degree from Harvard Medical School in 1900. He was a member of the staff of the St. Vincent Hospital. He was a fellow of the American Medical Association.

His widow, five sons, a daughter and three grandchildren survive.

**BUTLER** — John E. Butler, M.D., of Taunton, died March 9. He was in his eighty-second year.

Dr. Butler received his degree from Harvard Medical School in 1891. He was a retired Boston specialist in anesthesia.

His widow and a brother survive.

**ELIOT** — Henry W. Eliot, M.D., of Manchester, Vermont, died October 21, 1944. He was in his seventy-ninth year.

Dr. Eliot received his degree from the University of Vermont College of Medicine in 1898.

His widow survives.

**FISHER** — John C. V. Fisher, M.D., of West Roxbury, died February 20. He was in his fifty-third year.

Dr. Fisher received his degree from Boston University School of Medicine in 1917. Dr. Fisher served as a surgeon for the United States merchant marine during the first world war. He had practiced in Boston since 1919 and had been obstetrician at Massachusetts Memorial Hospitals since 1928. He was associate professor of obstetrics at Boston University School of Medicine. He was a fellow of the American College of Surgeons, and a member of the New England Obstetrical and Gynecological Society.

His widow and three daughters survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### RETURN OF EMPTY VIALS AND OUTDATED BIOLOGIC PRODUCTS

At the onset of the war emergency, the Antitoxin and Vaccine Laboratory was faced with serious difficulties in procuring containers, circulars and other supplies used in packaging biologic products. An appeal was sent out to physicians, boards of health and hospitals to return used packages or containers of biologic products to the laboratory so that these could be re-used. The return of outdated products, which has always been urged, was particularly stressed because of the wartime shortages of supplies and personnel.

The response has been gratifying. Thousands of outdated packages, empty containers and so forth have been returned. The containers have been re-used, and the products have been re-tested. Those products that could be salvaged have been re-processed and redistributed. These returns have aided tremendously in maintaining the continuity of production and distribution at the laboratory,

and this note is sent out to express the gratitude of the laboratory staff and of the department for the fine co-operation and assistance in this salvage program.

The situation regarding supplies and production is getting no better. Returns are needed as badly as ever and will continue to be welcomed. By returning empty containers and outdated products the physician and others not only help the war effort and save the taxpayers additional expense but also help to keep the supply of such products fresh and thus to avoid the risk of using supplies that are outdated.

### FLOODS AND TYPHOID VACCINATION

State and local health and welfare organizations, the American Red Cross and other agencies have already anticipated the possibility that serious floods will occur this spring as a result of the heavy snows of the winter. Although the recent extended thaws may have done much to reduce the likelihood of floods, the possibility remains that floods will occur, and plans must be made for handling the emergencies that may arise.

The organization of such programs in recent years has been developed largely in the Mississippi Valley and those of its tributaries — an area where typhoid fever is widespread and fairly prevalent. Consequently the administration of typhoid vaccine on a mass scale to persons in, or refugees from, flooded areas has become a widely accepted practice. In New England, however, the local conditions that prevail should be given serious study before accepting any such procedure simply because it has been widely used elsewhere.

Typhoid fever is a relatively rare disease in New England and consequently the risk of contamination of drinking waters because of floods is exceedingly slight. The application of mass immunization against typhoid fever is, therefore, not warranted in Massachusetts except in situations where there is sound reason to believe that typhoid infection may exist in the water supply in use. This is particularly true with the present shortage of health and medical personnel, for such immunization programs take a great deal of time and effort on the part of trained personnel, whose services may be more urgently needed in other ways. Another consideration is that the vaccine probably will not prevent the disease in persons already exposed by flood conditions.

If it is decided that vaccination is necessary, the program may be simplified by bearing in mind the value of a single dose of vaccine for anyone who has previously been vaccinated against typhoid fever. Such persons will obtain sufficient protection by receiving one dose of typhoid vaccine, given either as 0.5 cc. subcutaneously or as 0.1 cc. intradermally.

CONSULTATION CLINICS FOR CRIPPLED  
CHILDREN IN MASSACHUSETTS UNDER  
THE PROVISIONS OF THE SOCIAL SECURITY ACT

## CLINIC

## NOTES

Dr. J. G. McCallister

Dr. Joseph T. Wearn, at one time associate professor of medicine, Harvard Medical School, and associate director, Thorndike Memorial Laboratory, and visiting physician, Boston City Hospital, has recently been appointed dean of Western University School of Medicine, succeeding Dr. Torald H. Sollman, who retired last July. Dr. Wearn will continue as professor of medicine and director of the Department of Medicine, Lakeside Hospital, positions that he has held for a number of years.

†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

Alumps is quite prevalent though not up to the February record of 1942 and 1936. However, the number of cases is somewhat more than twice that representing the seven-year median.

Lobar pneumonia is again at a low point, the lowest on record for the month of February. The number of cases is approximately half that of the seven-year median.

Measles is at the lowest level reported for the month of February since 1907.

Scarlet fever shows a marked drop over the January record, and now is at about the seven-year average.

Pulmonary tuberculosis is tending to decline once more in spite of widespread case-binding activities.

interior polyomycetes was reported from: Boston, 1; Groveland, 1; Newton, 1; total, 3.

Diphtheria was reported from: Boston, 1; Framingham, 1; Hingham, 1; Lawrence, 1; Lowell, 1; Malden, 3; Medford, 1; New Bedford, 3; Northampton, 1; Sharon, 1; Taunton, 1; Worcester, 2; total, 17.

Dysentery, bacillary, was reported from: Gloucester, 1; Lexington (Metropolitan State Hospital), 7; Worcester, 1; total, 9.

Encephalitis, infectious, was reported from: Watertown, 1; total, 1.

Lymphocytic choriomeningitis was reported from: Swamp-

## RAPID DIAGNOSIS OF SMALLPOX

*To the Editor:* I have read with interest the editorial comment in the February 1 issue of the *Journal* on the work of Majors van Rooyen, Illingworth and Oliver, of the Royal Army Medical Corps. Certainly, if the conclusions put forward by these physicians are valid, they have made a major contribution to our knowledge of the vagaries of smallpox and, in addition, have added to our diagnostic armamentarium.

When I first read the report describing their methods for diagnosing smallpox as means from the skin lesions, I was quite impressed with the basic of characteristic elementary diagnosis of smallpox were adequate, despite the statement that appears in the text, "Every positive laboratory diagnosis was subsequently confirmed clinically." When the article by Majors Illingworth and Oliver, describing their clinical findings in smallpox in un in the Middle East came to my attention, however, it seemed that there was considerable room for improvement concerning the accuracy of the diagnosis of the laboratory because it was apparent that most of the material in which the original laboratory diagnosis was based was apparently not available to our diagnostic armamentarium.

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Meningitis, meningococcal, was reported from: Ashland, 1; Attleboro, 1; Boston, 9; Bridgewater, 1; Brockton, 1; Cambridge, 2; Chicopee, 1; Fitchburg, 1; Haverhill, 1; New Bedford, 1; Newton, 3; Springfield, 1; Taunton, 1; Westboro, 1; Worcester, 1; total, 26.  
 Meningitis, Pfeiffer-bacillus, was reported from: Brockton, 1; Everett, 1; Springfield, 1; total, 3.  
 Meningitis, pneumococcal, was reported from: Worcester, 1; total, 1.  
 Meningitis, undetermined, was reported from: Braintree, 1; Palmer, 1; Worcester, 1; total, 3.  
 Salmonella infections were reported from: Arlington, 1; Boston, 2; Revere, 1; total, 4.  
 Septic sore throat was reported from: Boston, 15; Newton, 1; Williamstown, 1; total, 17.  
 Trichinosis was reported from: Boston, 2; total, 2.  
 Typhoid fever was reported from: Adams, 1; Chicopee, 1; total, 2.  
 Typhulant fever was reported from: Hampden, 1; total, 1.

"In short, there was no single point, other than a positive vesicular scraping, which was entirely reliable for diagnosis."

I do not wish to dispute the facts that both smallpox and chicken pox can run very atypical courses and that at times each disease mimics the other, but I hesitate to accept as valid the findings of a new test to differentiate these two diseases when most of the evidence supporting the specificity of the test is based on the study of atypical cases of smallpox, which, except for the findings of the test, would have been called chicken pox.

I would be the first to admit that smallpox can occur in the vaccinated individual, but it is difficult to accept the diagnosis of smallpox in the series of 100 cases studied when all but 4 patients had been previously vaccinated and when 70 had been successfully vaccinated within a two-year period before onset. It is possible that what was read as an immune reaction to smallpox vaccination really represented a feeble response to impotent vaccine. In that event, of course, these persons were not successfully vaccinated. Furthermore, in contrast to the clinical description by these authors of mild smallpox, what little knowledge we do have of second attacks of the disease in the same person and bona-fide cases in vaccinated persons, indicates that, although the disease may be mild, the distribution of the lesions and their description, except for their number, do not differ strikingly from those occurring in the unmodified disease.

I approach this whole subject very much as a layman, since my knowledge of the laboratory aspects of the problem, as well as that of clinical smallpox, is meager. I do think, however, that my argument is pertinent and that additional evidence is needed before one can assume, on the one hand, that the 100 cases of smallpox described from Egypt actually were not, to a large extent, due to chicken pox and, on the other hand, that this interesting diagnostic test does clearly differentiate the two diseases. I intend to write the authors for additional information, but since your editorial has just come to hand, I thought it worth while putting my thoughts on paper for transmittal to you.

ROBERT F. KORN, M.D.  
Epidemiologist

State of New York Department of Health  
Division of Communicable Diseases  
Albany 1, New York

In the article by Majors Illingworth and Oliver one assumes that the difficulty in clinically recognizing the cases of smallpox was in the early stage, when they exhibited either the so-called "modified form," as a result of previous vaccination, or the violent hemorrhagic form, the onset of which sometimes suggests measles or typhus fever. Since these authors state that the positive findings in the scrapings of the early lesions were subsequently confirmed clinically, it appears that the later course of the disease established the diagnosis of smallpox. In addition, some of the more time-consuming laboratory tests may have been employed. As Dr. Korn points out, it is somewhat difficult to rationalize so many cases of smallpox, many of which were severe, in persons who had been successfully vaccinated. Possibly the "success" of the previous vaccinations, as he suggests, should be questioned, since it is well known that, for obvious reasons, vaccine virus stored in the subtropics and tropics is likely to lose its potency rapidly. Furthermore, even 96 cases in vaccinated persons are not particularly surprising when one considers the enormous number of troops that must have passed through this smallpox-infested country at the time that these observations were made. Certainly, any laboratory method by which it is claimed that smallpox can be rapidly differentiated from chicken pox deserves comment to ensure further study by other investigators. — Ed.

## NOTICES

### NEW ENGLAND HEART ASSOCIATION

The Henry Jackson Lecture of the New England Heart Association will be held at the Boston Medical Library on Monday, April 16, at 8:15 p. m. Professor Dr. Teosilo Ortiz Ramirez will speak on the subject "Heart Disease in Mexico, and the New National Institute of Cardiology," and the New National Institute of Cardiology are cordially invited to attend.

### JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a.m.

#### MEDICAL CONFERENCE PROGRAM

- Wednesday, April 4 — The Problem of Splenic Hemolysis. Dr. K. Singer.  
Friday, April 6 — Measurement of Hepatic Blood Flow. Dr. Stanley Bradley.  
Wednesday, April 11 — The Present-Day Concept of Streptococci and the Diseases Which They Produce. Dr. L. Weinstein.  
Friday, April 13 — The Diagnosis of Infections Due to Filterable Viruses. Dr. C. A. Janeway.  
Wednesday, April 18 — Penicillin in Venereal Disease. Dr. Oscar F. Cox.  
Friday, April 20 — Advances in Naval Medicine. Rear Admiral J. J. A. McMullin.  
Wednesday, April 25 — Treatment of Dermatoses. Dr. John G. Downing.  
Friday, April 27 — New Compounds for the Treatment of Hyperthyroidism. Dr. E. B. Astwood.

On Monday mornings (except April 9) clinics will be given by Dr. Samuel Proger. On Tuesday and Thursday mornings Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings clinics will be given by Dr. William Dameshek.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 5

##### FRIDAY, APRIL 6

\*9.00-10.00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10.50 a. m. Common Lesions of the Hand. Dr. Bernard Appel. (Post graduate clinic in dermatology and syphilology.) Amphitheater, Mallory Building, Boston City Hospital.

##### SATURDAY, APRIL 7

\*10.00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

##### MONDAY, APRIL 9

\*12.00 m.-1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

##### TUESDAY, APRIL 10

\*9:00-10:00 a.m. Medical clinic. Infants' Hospital.

\*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

##### WEDNESDAY, APRIL 11

\*12.00 m. Clinicopathological conference. Children's Hospital.

\*12.00 m.-1:00 p.m. Clinicopathological conference. Cambridge Hospital.

7:15 p.m. Graduate seminar in pediatrics. Children's Medical Service, Amphitheater 3A, Massachusetts General Hospital.

\*Open to the medical profession.

APRIL 4-27. Joseph H. Pratt Diagnostic Hospital. Medical conference program. Notice elsewhere on this page.

APRIL 5. New England Hospital for Women and Children. Page 364, issue of March 22.

APRIL 11. Tufts Medical Alumni Association. Page 364, issue of March 22.

APRIL 11. New England Dermatological Society. Page 364, issue of March 22.

APRIL 12. Progress in Dermatology as a Result of World War II. Dr. John G. Downing. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

APRIL 16. New England Heart Association. Notice elsewhere on this page.

APRIL 30. New York Institute of Clinical Oral Pathology. Page 334, issue of March 15.

JUNI 14-19. American Board of Obstetrics and Gynecology. Page 364, issue of March 22.

SEPTEMBER 17. American Public Health Association. Page 752, issue of November 30.

### DISTRICT MEDICAL SOCIETIES

#### PLYMOUTH

APRIL 26. Toll House, Whitman.

MAY 17. Lakeville Sanatorium, Lakeville

Meetings will be held at 11 a.m.

#### WORCESTER

APRIL 11. Hahnemann Hospital, Worcester.

MAY 9. Annual meeting.



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Number 14

## PAPAVERINE IN THE TREATMENT OF CORONARY-ARTERY DISEASE\*

WILLIAM GRAY, M.D.,† JOSEPH E. F. RISEMAN, M.D.,‡ AND SAMUEL STEARNS, M.D.§

BOSTON

**PAPAVERINE**, an opium derivative frequently used to combat vascular spasm, was first ad-

vocated for the treatment of angina pectoris in 1913 by Pail; no data were presented, however. Three years later, Maclat reported temporary relief of angina pectoris in 3 patients following injection of 40 mg. of papaverine. In 1923, Pail described prompt but transient relief of angina pectoris after the injection of 20 to 30 mg. of papaverine intra-venously in an eighteen-year-old patient with aortic stenosis and insufficiency; simultaneous in-

jections of larger doses were not so effective. In 1921, Boehm<sup>1</sup> reported marked success in treating patients with angina pectoris with 30 mg. of papav-erine in a mixture with camphor, given three times daily by mouth. In 1933, Evans and Hoyle<sup>2</sup> re-

ported that their studies on 31 patients offered no convincing evidence of the value of orally adminis-tered papaverine over other drugs tested. More re-

cently, interest has been stimulated by the work of Elek and Katz,<sup>3</sup> 12 of whose 17 patients showed definite improvement when given papaverine by mouth in doses of 100 mg. three times daily. Defi-

nite improvement was defined as a reduction of at least 25 per cent in the number of attacks, of 50 per cent in the duration of attacks and of 50 per

cent in the number of nitroglycerin tablets used, or an increase in the distance that the patient could

walk without pain. These authors stressed the im-

portance of using much larger doses of papaverine

than had previously been advocated.

All these investigators relied on clinical evalua-

tion of the efficacy of therapy. It has repeatedly

been shown that such methods fail to differentiate

the effects of inert and active therapy,<sup>4-12</sup> so that

objective studies are desirable. Such studies car-

ried out in this laboratory between 1935 and 1937

showed no change in the standardized exercise-

recorded, as was any unusual increase in ability to

walk without production of angina. On each visit

measured by the standardized exercise-tolerance

test, carried out in a cold room, as previously de-

scribed.<sup>14</sup> Many determinations of this tolerance

On each visit the patient was questioned care-

fully concerning the number of attacks of angina

pectoris experienced since the last visit, the number

of tablets of nitroglycerin used and the amount of

physical and emotional strain sustained during the

week. The patient's evaluation of the therapy was

were termed Group 3 patients.

no response to any of the usual forms of therapy and

Group 2 patients. The remaining 2 showed little or

moderate response to these drugs and were called

described<sup>15</sup> as Group 1 patients. Six showed a

classified in accordance with the method previously

sponse to nitroglycerin and other therapy and were

of study. Five showed a markedly beneficial re-

evaluated at frequent intervals during the period

vocated for angina pectoris was known and was re-

to respond to other types of therapy usually ad-

one to nine months. The ability of these patients

four to ten years, and the other 4 were observed for

Nine patients had been followed in the clinic for

6 had a history of myocardial infarction in the past.

angina pectoris for six months to fifteen years, and

to seventy-two years; 11 were men. All had had

visits to the Angina Clinic of the Beth Israel Hos-

studied in 13 patients who made regular weekly

The effect of papaverine in angina pectoris was

MATERIALS AND METHODS

doses recommended by Elek and Katz.<sup>3</sup>

ment of coronary-artery disease with the larger

five studies on the use of papaverine in the treat-

paper is to present the results of additional objec-

tive studies on the use of papaverine in the treat-

times a day.<sup>13</sup> All these patients had shown bene-

a fifth patient who received this dose orally three

injection of 30 mg. of papaverine in 4 cases, or in

tolerance test thirty minutes after the intravenous

were made while the patient was taking inert medication or placebos. The usual upper limit of tolerance while the patient was taking inactive medication was selected as a base line for comparison (Fig. 1).

On each visit the patient was given a supply of medication to be taken four times a day for at least one week. The results with papaverine hydrochloride\* (100 or 200 mg.) were compared with those with other medications, including placebos.

The effect of papaverine hydrochloride given intravenously was determined in the following manner while the patients were taking inert medication (enteric-coated lactose). A solution contain-

studies a control precordial tracing (Lead 4R) was taken with the patient standing at rest and also for fifteen seconds immediately after the cessation of exercise that induced an attack of angina. At a subsequent visit, identical studies were repeated after the administration of papaverine intravenously. To obtain such tracings, it was necessary for the patient to exercise with the electrodes in place and with the electrocardiograph running. In all cases the degree of RST deviation was measured as the average of ten consecutive complexes.

Clinical observations of the effect of 65 mg. of papaverine hydrochloride given intravenously for

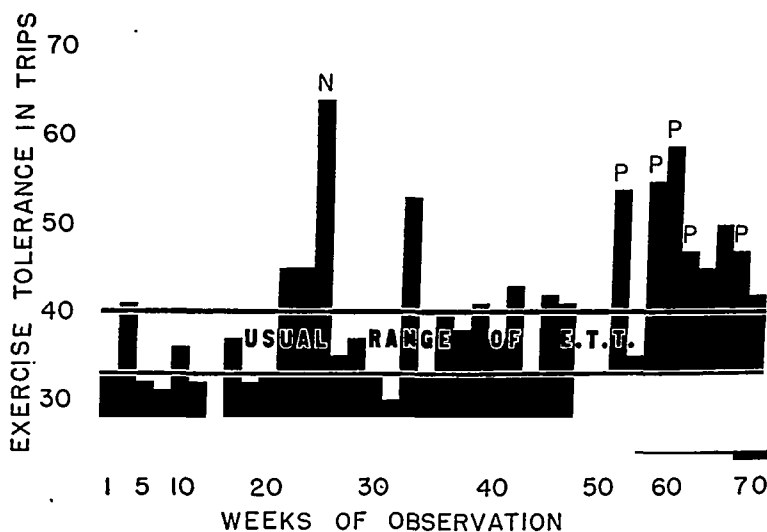


FIGURE 1. Studies of Standard Exercise Tolerance in Case 10 during a Period of 68 Weeks.

N indicates standard exercise tolerance after nitroglycerin, and P, after papaverine given intravenously. The medication during the period was as follows, according to weeks: 1-11, enteric-coated lactose; 12, 30 cc. whisky four times a day; 13-15, none; 16, 100 mg. Syntropan four times a day; 17-19, none; 20-23, enteric-coated lactose; 24-25, 0.3 gm. sodium bicarbonate four times a day (25, test, 2 min. after 0.3 mg. nitroglycerin); 26-33, 0.13 gm. Papaverine four times a day; 34, 0.2 gm. Theopropinal four times a day; 35-36, 0.3 gm. sodium bicarbonate four times a day; 37, 200 mg. papaverine hydrochloride orally four times a day; 38, 100 mg. Syntropan four times a day; 39, 30 mg. Prostigmin four times a day; 40, 1 gm. potassium chloride four times a day; 41, 2 gm. potassium chloride four times a day; 42-43, 0.3 gm. sodium bicarbonate four times a day; 44, 200 mg. ascorbic acid four times a day; 45-46, none; 47, 1.5 gm. physostigmin salicylate four times a day; 48-61, enteric-coated lactose (55, test, 15 min. after 65 mg. papaverine hydrochloride intravenously; 59, test, 5 min. after same dose; 60, test, 10 min. after same dose; 61, test, 30 min. after same dose); 62-64, none; 65-68, enteric-coated lactose (65, test, 10 min. after 100 mg. papaverine hydrochloride intravenously; 67, test, 15 min. after 100 mg. Octin subcutaneously; 68, test, 60 min. after 65 mg. papaverine hydrochloride intravenously).

ing 65 to 100 mg. of papaverine hydrochloride, usually diluted to 10 cc. with physiologic saline solution, was given intravenously, and the standardized exercise tolerance was measured at intervals varying from five to ninety minutes after injection. Each injection required about two minutes. Only one test was carried out on any given visit. The different doses used at varying time intervals served to check the results.

Electrocardiographic studies, according to the method previously described,<sup>12, 15</sup> were carried out in 2 patients who had shown a beneficial response to intravenously administered papaverine. In these

the relief of pain in 8 patients with acute myocardial infarction and in 3 with acute coronary failure were also made on the wards of the hospital. These patients varied in age from forty-nine to seventy-five years; 9 were men. In most cases, the solution of papaverine used was not diluted with physiologic saline solution.

## RESULTS

### Oral Administration in Angina Pectoris

*Clinical evaluation.* The effect of papaverine hydrochloride given by mouth was tested in 11 patients. There were twenty trial periods, in which 10 patients received 100 mg. and 10 received 200 mg.

\*The papaverine hydrochloride used in this study was furnished through the courtesy of Eli Lilly and Company, Indianapolis, Indiana.

tachycardia. In most cases these were not disturbing to the patients, but in 3 cases they were so severe that the patient refused to allow additional injections of the drug after two trials. Dilution with 10 cc. of physiologic saline solution permitted slower injection and decreased the severity of these reactions but did not eliminate them. In patients experiencing severe circulation-time reactions, transient nausea and sweating were frequent. Drowsiness lasting for about an hour followed each injection in 1 patient, but this was not severe enough to necessitate stopping injections. One patient received papaverine hydrochloride intravenously on two occasions during attacks of angina pectoris. On one of these the attack dis-

appeared in 5 patients. One (Case 13) was unable to take more than a single dose of the drug on each of two trials because of severe nausea. This patient had previously developed severe nausea necessitating cessation of therapy while taking Dilaudid (3 mg.) or morphine sulfate (8 mg.) by mouth. Two patients were unable to take doses of 200 mg. because of severe nausea, accompanied in 1 case by abdominal cramps, but were able to tolerate doses of 100 mg. Two patients developed slight nausea after 200-mg. but not after 100-mg. doses. No demonstrable clinical improvement occurred in any of the 10 patients able to tolerate papaverine by mouth (Table I). Only 1 patient (Case 1) stated

TABLE 1. *Clinical Evaluation of Papaverine Hydrochloride Given Orally.*

Case No	PLACEBO THERAPY			PAPABO THERAPY			THERAPEUTIC EFFECT†
	FREQUENCY OF PAIN*	TOXIC EFFECT	200-mg dose	FREQUENCY OF PAIN*	TOXIC EFFECT	200-mg dose	
Group 1:	1	•	•	1	•	•	Beneficial
	2	•	•	2	•	•	Beneficial
	3	•	•	3	•	•	Beneficial
	4	•	•	4	•	•	Beneficial
Group 2	5	•	•	5	•	•	Beneficial
	6	•	•	6	•	•	Beneficial
	7	•	•	7	•	•	Beneficial
Group 3.	8	•	•	8	•	•	Beneficial
	9	•	•	9	•	•	Beneficial
	10	•	•	10	•	•	Beneficial
	11	•	•	11	•	•	Beneficial
	12	•	•	12	•	•	Beneficial
	13	•	•	13	•	•	Beneficial
*Average number of attacks (or number of nitroglycerin tablets) per week							
†Patient unable to tolerate this dose							
According to patient							

curred in five to fifteen minutes after injection, with a slight effect persisting as long as sixty to ninety

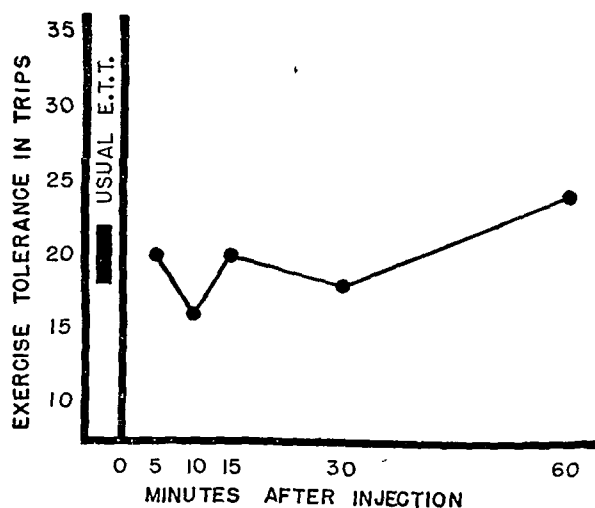


FIGURE 2. Case 7.

The chart shows the absence of increase in standardized exercise tolerance following the intravenous injection of papaverine hydrochloride.

minutes. There was no appreciable difference in results following doses of 65 or 100 mg.

*Electrocardiographic studies* were carried out in 2 patients who had shown a response to intravenous papaverine. In one, the RST segment, after twenty-six trips that produced an attack of angina, was depressed 3.0 mm. After the injection of 65 mg. of papaverine hydrochloride intravenously, the same amount of exercise failed to induce angina, and the RST depression was 2.1 mm. five minutes after injection, 2.5 mm. ten minutes after injection

injection of papaverine the same amount of work failed to induce angina and the RST depression was 2.0 mm.

#### *Intravenous Administration in Acute Myocardial Infarction or Coronary Failure*

Mild undesirable side effects were seen in 5 of the 11 cases studied. These consisted of slight dizziness in 1 case, nausea and vomiting in 1, drowsi-

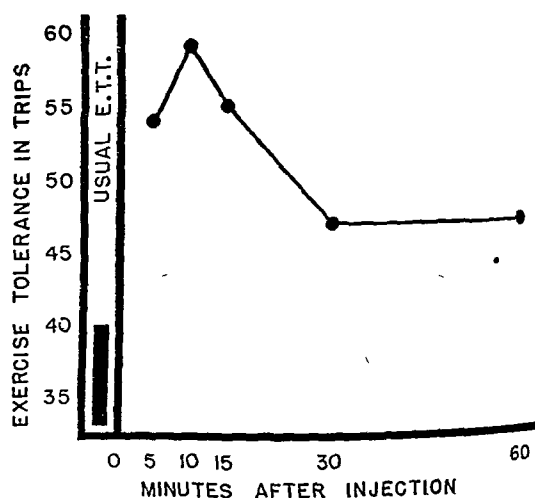


FIGURE 3. Case 10.

The chart shows an increase in standardized exercise tolerance following the intravenous injection of papaverine hydrochloride.

ness in 1 and moderately severe circulation-time reactions in 2. In general, even when the papaverine was not diluted with saline solution, the toxic effects in this group were not so severe as in the

TABLE 3. Objective Evaluation (Standardized Exercise Tolerance) of Intravenous Injection of Papaverine Hydrochloride.

CASE No.	PLACEBO THERAPY	DOSE	PAPAVERINE THERAPY							
			INTERVAL AFTER INJECTION							
	trips	mg.	5 min. trips	10 min. trips	15 min. trips	20 min. trips	30 min. trips	45 min. trips	60 min. trips	90 min. trips
<b>Group 1:</b>										
1	18-24	65	22+	31	28	—	30	—	24	—
2	22-26	65	35	35	33	—	33	31	31	30
3	43-52	100	—	34	—	—	—	—	—	—
4	25-32	65	49	35	38	—	51	—	35	—
5	24-28	65	—	44+	—	—	—	—	—	—
<b>Group 2:</b>										
6	20-24	65	22	22	20	—	—	—	—	—
7	18-22	100	—	—	23	—	—	—	—	—
8	28-36	65	20	16	20	—	18	—	24	—
9	25-32	100	—	20	22	—	—	—	—	—
10	33-40	65	38	—	32	—	—	—	—	—
11	25-32	65	36+	34+	46+	42+	—	38+	31	—
12	33-40	100	—	32+	—	—	—	—	—	—
13	33-40	65	55	59	54	—	47	—	47	—
14	33-40	100	—	45	—	—	—	—	—	—
15	14-19	65	—	24+	—	—	—	—	—	—
<b>Group 3:</b>										
16	22-28	65	20	—	—	30	—	—	—	—
17	24-30	33	26	—	—	—	—	—	—	—
18	24-30	65	21	—	—	—	—	—	—	—

+Indicates that angina was not produced. Exercise terminated because of fatigue or leg cramps.

and 2.0 mm. fifteen minutes after injection. Two minutes after the sublingual administration of 0.7 mg. of nitroglycerin, the RST depression was 1.2 mm. (Fig. 4). In the second patient, the RST depression during angina induced by thirty-four trips was 1.6 mm., and fifteen minutes after the

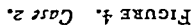
ambulatory less acutely ill patients with angina pectoris.

Sixty-five milligrams of papaverine hydrochloride given intravenously was followed by relief of pain in 5 of 8 cases of acute myocardial infarction and in 1 of 3 cases of coronary failure within forty

In most cases, seconds to two minutes of injection. In most cases, relief of pain occurred at about the same time as the circulation-time reaction. In 2 cases of myocardial infarction in which the previous administration of morphine and Dilaudid had been unsuccessful in relieving severe pain, the complete relief following injection of papaverine was dramatic. In a third case of myocardial infarction with severe pain, two 65-mg. injections of papaverine hydrochloride at ten-minute intervals afforded no relief, whereas morphine sulfate intravenously was beneficial. In 1 patient with coronary failure, the precordial pain became more severe during the injection of papaverine.

•

by mouth,



or 200 mg. four times daily for one week, is of little value in the clinical treatment of angina pectoris. This is demonstrated by the fact that none of the 11 patients studied were able to perform more work under standardized conditions after taking papaverine than they could do without the drug, and by the lack of significant clinical improvement. Larger doses are impractical because they cause gastric distress. These results are not in accord with those of Elek and Katz,<sup>6</sup> who first advised larger doses than had

distress.

The present series is admittedly small, but 9 of the 11 patients were able to do more work after effective drugs such as nitroglycerin. The patients received the drug for only one week at a time, for experience indicates that the response to vasodilator drugs occurs following each, even the first, dose. The effect of therapy over longer intervals is difficult to evaluate because periods of comfort, unrelated to therapy, are likely to be included. Another, probably more important, reason for the difference in results is that Elek and Katz relied on the history for evaluation of the effect. This method has

however, is of little value in the clinical treatment of patients with angina pectoris.

The oral administration of papaverine hydrochloride in doses of 33, 100 or 200 mg. to ambulatory patients did not improve their ability to exercise, and does not appear to be of practical value in the treatment of angina pectoris.

Studies in a small group of patients suggest that the administration of papaverine hydrochloride intravenously in doses of 65 or 100 mg. is of considerable value in treating the pain of coronary occlusion or coronary failure.

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# PLETHORA OF THE INTRACRANIAL VENOUS CIRCULATION IN A CASE OF POLYCYTHEMIA\*

## Pathologic Physiology and Diagnostic Considerations

JULIUS LOMAN, M.D.,† AND WILLIAM DAMESHEK, M.D.‡

BOSTON

**I**N POLYCYTHEMIA vera, symptoms referable to the head greatly outrank in incidence those relating to any other bodily system.<sup>1</sup> Actual cerebral vascular lesions are, furthermore, not infrequent. These include arterial or venous thromboses and hemorrhage, which is either intracerebral or sub-arachnoid in location. The development of extreme headache, amblyopia, papilledema and increased intracranial pressure in a case of well-marked secondary polycythemia led to studies that are of interest from the standpoint of intracranial dynamics, and to the conclusion that extreme plethora may result in changes indistinguishable from those occurring in other types of increased intracranial pressure.

## CASE REPORT

A. F. L., a 41-year-old male, was referred to the Joseph H. Pratt Diagnostic Hospital from the Boston Dispensary on October 2, 1942. He complained chiefly of severe headache and failing vision of 1 year's duration. Since the age of 10, he had suffered from severe perennial asthma, with frequent attacks lasting as long as 12 hours. On several occasions he had had small hemoptyses, which were usually associated with a dull aching sensation in the chest. In recent years, he had been completely incapacitated because of increasing exertional dyspnea. For the past year the vision had become increasingly blurred, and was frequently associated with scintillating scotomas and small black spots

before the eyes. Beginning about a month before admission, the patient developed a continuous and severe occipital headache that was unassociated with nausea or vomiting and unrelieved by aspirin. For 2 weeks there had been occasional staggering with walking.

Examination disclosed an extremely cyanotic man, lying flat in bed without much respiratory distress. The eyeballs were somewhat prominent. The pupils were round and equal and somewhat dilated, and reacted poorly to light and accommodation. The vessels of the scleras were deeply injected. The conjunctivas were deep purple. The retinal vessels, particularly the veins, were greatly distended. Both optic disks showed pronounced choking, particularly marked over the nasal halves. Numerous pinpoint hemorrhages were scattered throughout both fundi.

The anteroposterior diameter of the thorax was greatly increased, with very limited excursion, respirations being almost entirely abdominal. The percussion note was hyperresonant throughout, with complete absence of absolute cardiac dullness. Numerous sonorous and sibilant rhonchi and occasional crepitant inspiratory rales were heard. The heart sounds were distant and heard only over the xiphoid cartilage. There were no murmurs. The blood pressure was 135/90. There was marked distention of the veins in the upper extremities, and large varicosities were present bilaterally. The fingers were not definitely clubbed. Neurologic examination showed intact cranial nerves, active and equal reflexes of the arms, and knee jerks that were equal but barely obtainable on reinforcement. Ankle jerks were equal and active. There was an equivocal Babinski sign on the right and definite Babinski and Chaddock signs on the left. There was no ankle clonus.

The urine showed a +++ test for albumin and a few hyaline and fine granular casts in the sediment. The specific gravity was 1.018, and there was good concentration with a modified Fishberg test. The blood findings were as follows: hemoglobin, 136 to 142 per cent (21.1 to 22.0 gm.); reticulocytes, 0.3 per cent; red-cell count, 8,100,000 to 9,000,000; white-cell count, 6500 and 7400, with 69 per cent polymorphonuclear leukocytes, 14 per cent lymphocytes, 10 per cent

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‡Professor of clinical medicine, Tufts College Medical School; visiting physician and hematologist, New England Medical Center.



Increased intracranial pressure has occasionally been noted in true polycythemia, and has at times led to the false diagnosis of intracranial neoplasm and even to surgical exploration. The mechanisms of the increased pressure have never been worked out. In the present case, although the increased pressure was obviously related to the effects of the

rather than to actual thrombosis of the cerebral venous channels. With thrombosis of a lateral sinus, one would expect either low or absent pressure in the corresponding internal jugular vein. At the point at which the internal jugular pressure is measured the vein is contiguous to the outlet of the jugular bulb, where it receives no venous con-

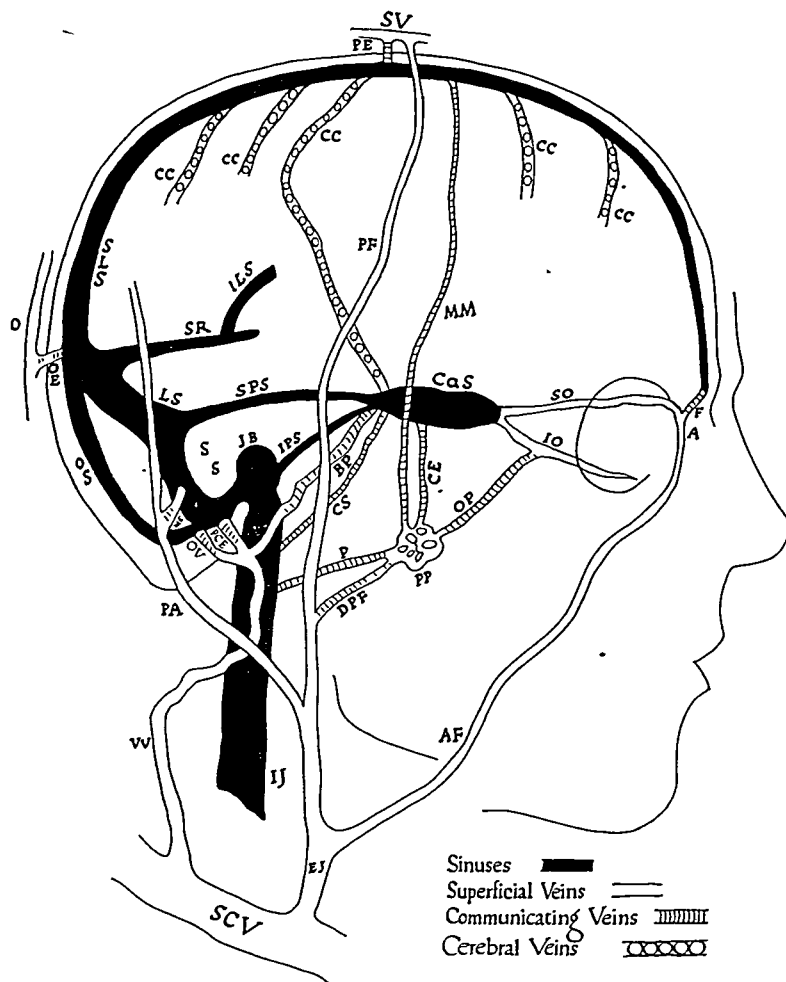


FIGURE 2. Diagram Showing the Communications between the Dural Sinuses, the Cerebral Veins and the Superficial Veins (Modified from Braun<sup>12</sup>).

A, angular vein; AF, anterior facial vein; BP, basilar plexus; CC, superior cerebral veins; CE, communication between cavernous sinus and pterygoid plexus; CaS, cavernous sinus; CS, communication between cavernous sinus and internal jugular vein; DPF, deep posterior facial vein; EJ, external jugular vein; F, frontal vein; IJ, internal jugular vein; ILS, inferior longitudinal sinus; IO, inferior orbital vein; IPS, inferior petrosal sinus; JB, jugular bulb; LS, lateral sinus; ME, mastoid emissary; MM, middle meningeal vein; O, occipital vein; OE, occipital emissary; OP, communication between infraorbital vein and pterygoid plexus; OS, occipital sinus; OV, communication between occipital sinus and vertebral vein; P, pharyngeal vein; PA, posterior auricular vein; PCE, posterior condyloid emissary; PE, parietal emissary; PF, posterior facial vein; PP, pterygoid plexus; SLS, superior longitudinal sinus; SCV, subclavian vein; SO, supraorbital vein; SPS, superior petrosal sinus; SR, straight sinus; SS, sigmoid sinus; SV, scalp vein; VV, vertebral vein.

disease, it was at first debatable whether this was due to cerebral venous thrombosis or to simple plethora of the intracranial venous system. The information gained by measurement of the pressure and the dynamic responses within the internal jugular circulation, together with the great diminution of the intrajugular pressure following several venesections, almost certainly pointed to the presence of plethora

tributaries. Furthermore, if lateral sinus thrombosis were present, jugular compression would effect no rise in the contralateral jugular pressure. In this case the jugular pressure was not only equally high bilaterally but was increased by homolateral and contralateral jugular compression.

It is furthermore doubtful whether a simple thrombosis of the lateral sinus is sufficiently ob-



changes in pressure. When, however, the venous circulation is already overtaxed, as in polycythemia, it is possible that further slowing, in some cases to the point of thrombosis, may be enhanced by these peculiarities of the intracranial venous system and result in a great increase in cerebral venous pressure. Another possibility that must be considered in any dissociation of the cerebral and the general venous pressure is the presence of an obstructing lesion of the neck or mediastinum, with compression of the great veins. There was no evidence of such an abnormality in the present case. It is furthermore obvious that a rise in cerebral venous pressure by this type of obstruction could not be relieved by venesection alone.

#### SUMMARY AND CONCLUSIONS

A case is reported of severe secondary polycythemia with increased intracranial pressure, choked disks and amblyopia, in which dissociation between an increased internal jugular venous pressure and a normal general venous pressure was present. Following venesection therapy, the cerebral fluid pressure and intrajugular venous pressure became normal, and there was complete regression in all the symptoms referable to the head. The possible mechanisms for the dissociation between intrajugular and general venous pressures, with the resulting great increase in cerebrospinal fluid pressure, are discussed. Other possible causes of this dissociation, including thrombosis of the lateral sinus, are discussed, and excluded as having no bearing in the present case. A study of the intrajugular dynamics may be diagnostic in the determination of the presence or absence of thrombosis of the lateral sinus. Severe headaches in polycythemia may be caused by an increased intracranial venous pressure, with a resultant increase in cerebrospinal fluid pressure.

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destructive to the outflow of the intracranial blood to jugular veins or both lateral sinuses, the cerebrospinal fluid pressure returns to normal within a few hours. Furthermore, Hassin<sup>11</sup> has shown that thrombi that completely obstruct both the longitudinal and lateral sinuses have no effect on the absorption of the cerebrospinal fluid from the subarachnoid space; it is probable that under such conditions veins other than the longitudinal sinus are capable of absorbing the cerebrospinal fluid and keeping its pressure at normal values. In addition, if such vascular lesions were present, a return to a normal intracranial pressure should not be expected so soon after venesection. The likeliest explanation of the increased intracranial pressure in the case under discussion is therefore a great increase in cerebral venous pressure. This could be brought about by slowing and damming of venous blood in the rigidly enclosed sinuses and cerebral veins. The resulting increases in venous pressure would readily be reflected to the cerebrospinal fluid by way of the thin-walled cerebral veins. The dissociation between the pressure in the internal jugular vein and that in the general venous system in the absence of obstruction to cerebral venous channels is a unique phenomenon. So far as we know, no other examples have been reported. Certain physical conditions unique to the intracranial cavity may predispose to such a dissociation in pressures. Thus the cerebral veins have features that differ in certain particulars from the veins elsewhere in the body. These may be listed as follows: complete rigidity of the cranial venous sinuses; lack of muscular fibers in the walls of the sinuses; great width of the lumens of the sinuses as compared with the small size of the veins that empty into them; entrance of the many cerebral veins into the longitudinal sinus against the current of blood flow; and tortuosity of the course of the sinuses. In the last, the longitudinal sinus splits at right angles at the torcula. The inferior part of the sigmoid sinus lies at a much lower level than the jugular bulb, which is much wider than the sigmoid sinus. As the sigmoid sinus enters the jugular bulb, there is a marked narrowing. There is also a marked narrowing at the exit of the jugular bulb (Fig. 2). These characteristics seem designed to retard the flow of blood so that under certain conditions, such as sudden changes in posture, the brain is spared the sudden and full brunt of extreme vascular

## PSYCHOSOMATIC INTERRELATIONS IN GENERAL MEDICINE

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LOWELL, MASSACHUSETTS

THE efficiency of the general medical practitioner is conditioned by the following factors: first, his knowledge and appreciation of the normal human organism as a complex and integrated whole of physical, mental and emotional elements and his understanding and appreciation of the types of pathologic variations from normality that may arise, with their respective symptomatology and etiology; second, his knowledge of how to determine the nature and extent of these variations; and third, his selection of treatment.

Knowledge and appreciation of the normal human organism of integrated physical, mental and emotional elements include the following concepts: the body as a mechanism made up of cells performing proper physiologic functioning; the nervous system, of which the brain is the integrating center and through which activity of the biologic organism functions from within in a relation compatible to its environment; consciousness, the main function of the brain through which the mind is made rationally aware of the motivating biologic forces in the organism; the emotions, serving as well-balanced, subjective feeling-reactions to perception of these forces; personality, or the subject's usual manner of handling these forces in accordance with his best social adjustment; thoughts and ideas, which are concepts arising from these forces as highly developed adaptations of them to the environment; conscience and ideals, or the ethical and esthetic resultants arising from the mental and emotional conditioning of these forces; and the normal life of the normal human organism, which essentially consists in satisfying these forces — needs, urges and responses — in accordance with conscience and ideals.

An attempt has been made through this brief analysis of the normal human organism, with its balanced, co-ordinated psychosociobiologic functioning, to establish the concept of it as a complex and integrated whole.

Consideration of the pathologic variations that may occur in the normal human organism, with their respective symptomatology and etiology, includes the concepts of pathologic disturbances ranging from trauma of cellular tissue to tensions in the highest levels of the brain. If emotional tensions affect the lower levels of the nervous system and are mediated through the autonomic system, they cause a disturbance called "organ neurosis." In this condition the somatic component is the most pronounced element. If emotional tendencies develop and affect the highest levels of the brain, they cause neurotic and psychotic disturbances, which

are evidenced in thought and behavior. In these cases the psychic symptoms are most evident. Any disruption of balanced, co-ordinated psychosociobiologic functioning in the human organism results in its disintegration or in a pathologic condition.

Clinical study has revealed that in the investigation of functional disturbances there are specific correlations between emotional constellations and physiologic responses. The psychosomatic conditions resulting from these functional disturbances are called "psychosomatic symptoms."

Psychosomatic symptoms are present in all disease. Their psychic and physical components are in direct ratio to the degrees of psychologic and physical etiologic forces involved. Menninger<sup>†</sup> has classified disease in five groups, and indicates the relative degrees of symptomatic expression in terms of psychic reaction and physical reaction for each group. In Group 1, with a valence of 5 on the psychic reaction and a valence of 1 on the physical reaction, are included all the severe functional mental diseases referred to as psychosis. In Group 2, with a valence of 4 on the psychic reaction and a valence of 2 on the physical reaction, is included a class of illnesses generally regarded as mental in that the causative factors are chiefly psychologic but are always associated with physical symptoms, which are often treated as if they were the sole causes. In Group 3, with a valence of 3 on the psychic reaction and a valence of 3 on the physical reactions is included a heterogeneous assortment of diseases — first, organic brain diseases; second, the endogenous toxic and infectious illnesses in which the mental symptoms are produced by toxins; and third, a host of physical diseases that masquerade under the guise of mental symptoms, often appearing to be primarily mental. In Group 4, with a valence of 2 on the psychic reaction and a valence of 4 on the physical reaction, is placed a large class of organic illnesses frequently found in persons in whom are discovered conspicuous psychologic maladjustments but whose complaints are physical and whose diseases are manifested in organic disease. In Group 5, with a valence of 1 on the psychic reaction and a valence of 5 on the physical reaction, are found a great number of illnesses in which almost the entire emphasis seems to be on the somatic side but in which the psychic component, even though inconspicuous, is of great importance.

If the concepts of the human organism as an integrated whole and of disease as the psychosomatic expression of this biologic unit are accepted, the general medical practitioner must seek the etiology

<sup>†</sup>Menninger, W. C. *Psychological factors in disease*. *Wisconsin M. J.* 37:29-38, 1938.

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of disease in the constitution and in exogenic, psychologic and social factors. Until recent times the training that most physicians received failed to include any practical, systematic knowledge of such therapeutics. Consequently, many of those who can find no organic disease in a patient attempt to convince him that he is suffering only from "tired nerves" or "imagination." The dissatisfied patient who has received such a diagnosis seeks the services of physician after physician. Each in turn gives him a similar interpretation, none considering factors other than somatic symptoms to be pertinent to his condition.

The following three illustrations, similar to cases in the everyday experience of the general medical practitioner, bear out the truth of the above statements. In each of them the patient had consulted several physicians and had been given only drug therapy.

CASE 1. H. S., a 45-year-old man, with a wife and five children, had been unemployed and unable to secure employment for a period of 11 months. He complained of gastric pain 1½ hours after eating; this condition was relieved only by taking more food or by alkaline therapy. His symptoms were a very poor appetite, insomnia and marked loss of weight, due to restricted diets given by various clinics and physicians. X-ray examination showed an ulcer situated near the pyloric end of the stomach. The patient was given various kinds of alkaline drugs, to no avail. During consultations the fact became evident that extreme worry over his financial situation was responsible for many of his symptoms. Employment was secured for him. In less than a month his condition was normal in every respect, and it has remained so for over 15 years.

CASE 2. An 80-year-old man was confined to bed suffering with a peritonist-like abscess. The treatment given failed to effect a spontaneous cure, so that he became convinced that the attending physician could do nothing for him. He insisted that he had carcinoma of the throat and that no one would tell him the truth. He refused food and medication, wishing only to hasten his end so that he might be spared pain. He lost 30 pounds in 2 weeks. He finally consented to consult a nose-and-throat specialist, who after examining him remarked that what he could see was "all right" but that there was possibly "something lower down in the larynx." The physician suggested an x-ray examination, which was made. The patient insisted on telling the roentgenologist exactly where to look and what to do. After being assured that there was no disease in his throat and that an enlarged uvula caused the tickling and cough, the patient returned to his home, where he was given a sedative for one night's sleep and placed on a high-calorie and high-vitamin diet. His recovery was rapid and complete.

CASE 3. An extremely nervous and emaciated 15-year-old girl, who was a bed patient, complained of nausea, vomiting, pain over the lower abdominal region, constipation and scanty and irregular menstrual periods. Repeated enemas brought no relief. The patient lived with her family, the members of which were neurotic. Physicians had referred her to a surgical service, where she had been told that she must undergo an operation if she wished to live. She became hysterical. Since no diagnosis calling for surgery had been given, the attending physician decided on medical treatment. After elevation of the foot of the bed to help the abdominal organs to rise out of the pelvis, regulation of the diet and the giving of clyses to restore the lost body fluid and of sea moss and mineral oil for the constipation, vomiting stopped in 1 week and the patient became free from pain and much more cheerful. A prosthetic belt was used to hold up the organs until she gained weight. The physician established a situation

## SUMMARY

The normal human organism is a psychosociobiologic whole, and any disruption of the co-ordinated functioning of this whole results in a pathologic condition, which is evidenced by psychosomatic symptoms. The general medical practitioner should be able to recognize these psychosomatic symptoms, to make the correct diagnosis and to apply proper treatment. Current practice in medicine should include the use of psychiatry, since only in this way can the psychic and the somatic components in a patient be studied in their proper relation.

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In all these cases the abnormal condition was chiefly due to a personality disorder, but the psychic component of these conditions had been disregarded. Since 50 per cent of the cases coming to general medical practitioners may be placed in this group of so-called "biologic functional disorders," the urgent need for the revision and expansion of modern medicine in postgraduate and undergraduate medical education is evident.

Medical colleges must provide for the training and education of all physicians in the field of personality disorders, including their recognition, their symptomatology, their scientific treatment and their prevention. Such training and education demand the inclusion of psychiatry as a basic medical subject and the compulsion of everyone practicing medicine to become as firmly grounded in this field as he is in other basic medical subjects.

Orientation courses in psychiatry, dealing with the emotional factors in the general medical and surgical patients in whom the symptoms of functional illness are most frequently encountered, should be given for the benefit of those medical practitioners who have little knowledge of or training in psychiatry and psychiatric technique. Only when anatomy, physiology and the chemistry of the body are studied in relation to biologic functioning can a true diagnosis of its pathologic variations from normality be made and proper therapeutic treatment be applied.

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# PREPARATION OF SOLUTIONS

For clinical administration penicillin is usually dissolved in physiologic salt solution, although distilled water and 5 per cent dextrose solutions are also satisfactory solvents. Penicillin is extremely soluble and the concentrations employed can be varied with the method of administration, for example, from 250 units per cubic centimeter for local application to superficial wounds to 100,000 units per cubic centimeter when large doses are being given intramuscularly. For intramuscular use a concentration of 5000 units per cubic centimeter permits the giving of doses up to 15,000 units without undue discomfort, and the amount of drug lost by the adherence of the solution to the bottle and syringe and in other unavoidable ways is less than when higher concentrations are used. Since penicillin solutions are not self-sterilizing, care should be taken to avoid contamination while the solutions are being prepared and administered.

## PHARMACOLOGY AND METHODS OF ADMINISTRATION

Early studies of the pharmacologic properties of penicillin by Florey and his associates<sup>10</sup> and by Rammelkamp and Keefer<sup>11</sup> indicated that certain inconveniences would have to be contended with in the clinical administration of penicillin. Oral administration was found to be ineffective because the drug so given was largely inactivated by the hydrochloric acid of the gastric juice. Many ingenious attempts have been made to overcome this difficulty, but no effective method of administering the drug orally in moderate doses has yet been discovered.<sup>12</sup> The rectal instillation of penicillin was also found to be ineffective because the drug was rapidly inactivated by the intestinal bacteria.

Fortunately it was found that penicillin could be administered intravenously or intramuscularly without untoward reactions and that effective blood levels could be achieved when the drug was so administered. The same studies revealed, however, that owing to the rapid excretion of penicillin in the urine, blood levels were not well maintained. In patients with normal renal function about 60 per cent of the amount injected was excreted in the first hour. This rate of excretion was found to vary little, if at all, with the size of dose administered, although with large doses detectable concentrations of penicillin in the blood persisted longer than with small doses. Thus, when large doses, such as 50,000 and 100,000 units, were given in a single injection, small amounts of drug were found in the blood for as long as four to six hours. Fleming et al.<sup>13</sup> have pointed out, however, that a continuous bacteriostatic level can be obtained in the blood much more economically by the use of small doses, such as 15,000 units, given every two or three hours than by the administration of large doses at only

slightly longer intervals, and this has been confirmed by clinical experience.

After the intramuscular injection of a given dose, an effective blood level was found to be maintained for a slightly longer period of time than after the intravenous injection of a similar quantity of drug. This observation, together with the greater ease of administering the drug intramuscularly, led most workers both in England and in the United States to follow the Florey's<sup>14</sup> in using the intramuscular route for the routine treatment of patients. It is now well established on the basis of clinical experience that this route is fully as effective therapeutically as the intravenous route.

Early attempts to administer the drug subcutaneously revealed that absorption from the subcutaneous tissues was slow and irregular,<sup>11</sup> and in addition it was found that subcutaneous injection was often quite painful. More recently it has been reported that absorption after subcutaneous administration does not differ significantly from absorption after intramuscular injection.<sup>15</sup> It is likewise stated that with the present preparations of penicillin, subcutaneous injection is not significantly more painful than is intramuscular injection. Herwick et al.<sup>16</sup> have shown that there is a significant correlation between the purity of a penicillin preparation and the irritation resulting from its intramuscular injection. It is therefore not unlikely that, becomes available, the subcutaneous administration of the drug may be more widely practiced.

Several attempts have been made to obviate the need for frequent injections and the irregular blood concentrations that result from this method. Admixing penicillin by a continuous intravenous infusion has been the method most frequently used. Some investigators<sup>17</sup> believe that this is the method of choice and use it routinely. Other workers<sup>18, 19</sup> think that the inconveniences encountered in maintaining a constant intravenous infusion, together with the fairly frequent development of painful thrombophlebitis, outweigh its possible advantages. More recently the use of a continuous intramuscular infusion has been recommended.<sup>19</sup> The total twenty-four-hour dose of penicillin can be administered in a volume of 200 cc. to 500 cc. without undue discomfort into the lateral muscle of the thigh, and quite uniform blood levels can be maintained.<sup>20</sup> The levels achieved by this method are approximately the same as those obtained by the continuous intravenous infusion of the same dosage of penicillin.

Two other methods designed to reduce the number of injections have recently been reported. Romanovsky and Rittman<sup>21</sup> have stated that mixtures of penicillin in beeswax and peanut oil, when injected intramuscularly, are slowly absorbed and that therapeutic levels of penicillin can be detected

## MEDICAL PROGRESS

## THE TREATMENT OF INFECTIONS WITH PENICILLIN\*

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**P**ENICILLIN is now well established as an effective chemotherapeutic agent for the treatment of many infections. During the past year so many reports attesting to this fact have appeared in the American and English literature that to review them all in a single paper is not possible. The purpose of the present article is to summarize such principles of penicillin therapy as have evolved from the investigations of the past five years and to present the current views on the use of penicillin in the more important infections that are encountered in civilian practice. It is recognized that experience with penicillin is enlarging so rapidly that some or many of these views may be outdated before this article reaches print.

The history of the discovery of penicillin by Fleming<sup>1</sup> in 1928 and of its later development as a practical chemotherapeutic agent by Florey and his associates<sup>2</sup> is now well known by the medical profession and will not be reviewed. Likewise, it is beyond the scope of this paper to recount the fascinating story of how the large-scale production of the drug was achieved in the face of many difficulties.<sup>3, 4</sup>

## CHEMISTRY

The published information regarding the chemistry of penicillin is meager. Abraham and Chain<sup>5</sup> have reported that penicillin is an organic acid. Since the free acid is quite unstable, however, only the more stable sodium and calcium salts of penicillin are prepared for clinical administration. These two salts do not differ in therapeutic activity or toxicity. The calcium salt has the advantage that it is less hygroscopic and therefore can be used in powdered form with greater ease.

It is now known that the mould *Penicillium notatum* actually produces several types of penicillin. Sir Henry Dale<sup>6</sup> has recently revealed that three penicillins have already been isolated in the pure state. These are known in the United States as penicillins F, G and X, and in England as penicillins 1, 2 and 3, respectively. Dale states: "All these penicillins have the specific remedial action in high,

though not quite identical degrees, and there are proportional differences, still to be explored, in their proportional efficiencies against different infective organisms. Penicillin G or 2 is the penicillin which is predominant in most preparations now available." Penicillin G was the first to be obtained in pure crystalline form, the isolation of the crystalline sodium salt being accomplished by MacPhillamy and Wintersteiner of the Squibb Institute in July, 1943.<sup>3</sup> This material was found to contain about 1650 Oxford units per milligram.†

Recently the International Conference on Penicillin<sup>7</sup> has recommended that an international penicillin standard be prepared from crystalline sodium penicillin G and that the international unit of penicillin be defined as the specific penicillin activity contained in 0.6 micrograms of the international penicillin standard. The international unit so defined is approximately equivalent to the Oxford unit.

Although pure crystals of penicillin were first isolated almost two years ago, synthesis of the drug has not yet been accomplished. All the drug produced today is recovered from culture liquor in which *P. notatum* has grown. Because a large amount of active drug is lost in preparing crystalline penicillin, this material is not available at present for the routine treatment of patients. The preparations that are used in clinical practice assay roughly between 200 and 1000 Oxford units per milligram. It is thus evident that they contain between 37 and 88 per cent of impurities.

The preparations of penicillin that were first employed clinically were found to be relatively unstable both in powder form and in solution. The more recently prepared commercial products are a great deal more stable. Kirby<sup>8</sup> has shown that solutions of penicillin may be kept at room temperature (22° C.) for one week without evidence of deterioration and that most lots of penicillin retain their full activity in solution for ten to twelve days. At 37° C., however, full potency persists for only four days. As a dried powder the drug is even more stable. Regna's<sup>9</sup> studies indicate that there is no loss of potency during a period of at least three hundred and fifty days when the powder is stored at 0-5° C. Even at 37° C. the powder will retain full potency for at least sixty days.

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†Chemical assay of penicillin is not yet possible. The drug is assayed therefore in terms of its antibacterial activity. The Oxford unit is defined as "that amount of penicillin which, when dissolved in 50 cc. of meat-extract broth, just completely inhibits the growth of the test strain of *Staphylococcus aureus*."

32 guinea-pigs treated with penicillin and a mortality rate of 91 per cent in an equal number of untreated controls. Augustine et al.,<sup>37</sup> also using guinea pigs, found penicillin had no curative value after the appearance of clinical manifestations of the disease.

The action of penicillin on viruses and rickettsia is likewise not wholly clear. Hellman and Herrell<sup>38</sup> have reported that mice infected with the viruses of ornithosis and psittacosis can be protected by penicillin, whereas Morgages, Pinkerton and Greiff<sup>39</sup> have shown that penicillin therapy reduces the mortality in mice infected with murine typhus fever. In both studies the dosage per kilogram of body weight was far in excess of that necessary in clinical practice to control infections caused by susceptible bacteria. To date no convincing reports have been published to indicate that penicillin is effective in any virus or rickettsial disease in man. When such infections are complicated by secondary infections due to organisms that are sensitive to the drug, the latter may be successfully treated with penicillin.<sup>40</sup> In contrast to the susceptible species, many important pathogenic bacteria are not adversely affected by the concentrations of penicillin that can be achieved in the blood and tissues (Table 2).

TABLE 2. *Organisms Not Susceptible to the Action of Penicillin.*

<i>Escherichia coli</i>	<i>Haemophilus ducreyi</i>
<i>Escherichia typhosa</i>	<i>Streptococcus faecalis</i>
<i>Shigella dysenteriae</i>	<i>Brevella meliensis</i>
<i>Salmonella paratyphi</i>	<i>Vibrio cholerae</i>
<i>Salmonella enteritidis</i>	<i>Pasteurella pernis</i>
<i>Pseudomonas aeruginosa</i>	<i>Pasteurella tularensis</i>
<i>Klebsiella pneumoniae</i>	<i>Mycobacterium tuberculosis</i>
<i>Haemophilus influenzae</i>	<i>Plasmodium falciparum</i>
<i>Haemophilus pertussis</i>	<i>Xerosis</i>
	<i>Molds</i>

It is now well known that *Escherichia coli* and certain other bacteria insensitive to penicillin produce a substance that inactivates penicillin. This substance has been named "penicillinase."<sup>41</sup> Penicillinase can be prepared by various means,<sup>42-45</sup> and its incorporation in culture mediums to inactivate penicillin present in the blood and exudates of patients receiving the drug has been suggested. Experience, however, does not indicate that penicillinase has the same practical value that *p*-aminobenzoic acid has in inhibiting sulfonamide activity in culture mediums. Thus, when duplicate cultures with and without penicillinase are made, the number of additional positive cultures obtained is insignificant.<sup>46</sup>

Several different methods have been described for determining the concentrations of penicillin in the blood and body fluids.<sup>32-34</sup> All these methods involve the titration of the antibacterial activity of the unknown specimen against an organism of known sensitivity to penicillin. Although such methods are admittedly crude, they permit an estimation of penicillin concentration that is satisfactory for clinical purposes. The equipment and technical skill necessary to perform these tests are not beyond the reach of the average bacteriologic laboratory, but the information that is gained does not seem to be sufficiently helpful to warrant the routine determination of penicillin blood levels in clinical practice. The clinical response to treatment is, in most cases, all that is needed to determine dosage. A somewhat more useful test for clinical purposes is the determination of the sensitivity of various organisms to penicillin.<sup>47</sup> In the great majority of cases one can rely on the bacterial species alone as an indication of susceptibility. In particular cases, however, especially those that do not respond to penicillin in the expected manner, determination of the susceptibility of the patient's organism to penicillin is of value.

These species are generally considered to be insensitive to penicillin. Actually several of these species can be inhibited in vitro by the use of relatively high concentrations of penicillin, indicating that penicillin insensitivity is often a relative rather than an absolute quality.<sup>41</sup> For practical purposes, however, it is recognized that penicillin has no effective clinical action against these organisms.

The development of resistance to penicillin by bacteria as the result of exposure to sublethal concentrations of the drug either in vitro or in vivo has been reported by several workers.<sup>48-50</sup> There is some laboratory evidence to indicate that organisms that develop resistance to penicillin in vitro may become less virulent.<sup>44, 45</sup> Observations of this kind have not yet been made in human infections. The antibacterial action of penicillin in vitro may be either bactericidal or bacteriostatic.<sup>46</sup> Most human infections are agreed that in the treatment of penicillin inhibits the growth and multiplication of bac-



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terria, but the actual destruction and elimination of the infecting organisms are probably effected by the normal defense mechanisms of the host. This conclusion is well substantiated by clinical experience. With the exception of uncomplicated gonorrhoea and meningococccemia, treatment with penicillin has not proved to be effective in any disease unless it has been continued for at least twenty-four to forty-eight hours, and in the great majority of cases much longer periods are necessary. Florey et al.<sup>10</sup> early reported that serum, pus, exudates and the breakdown products of tissue autolysis do not inhibit the action of penicillin, a distinct advantage for this drug over the sulfonamides in many types of infection. Bigger<sup>11</sup> has recently reported that human serum does inhibit the action of penicillin. He attributes this phenomenon to the absorption of penicillin inactivators formed in the intestinal tract. It is now well known that *Escherichia coli* and

It is now well known that *Escherichia coli* and certain other bacteria insensitive to penicillin produce a substance that inactivates penicillin. This substance has been named "penicillinase."<sup>43</sup> Penicillinase can be prepared by various means,<sup>43-45</sup> and its incorporation in culture mediums to inactivate penicillin present in the blood and exudates of patients receiving the drug has been suggested. Experience, however, does not indicate that penicillinase has the same practical value that *p*-aminobenzoic acid has in inhibiting sulfonamide activity in culture mediums. Thus, when duplicate cultures with and without penicillinase are made, the number of additional positive cultures obtained is insignificant.<sup>20</sup>

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32 guinea-pigs treated with penicillin and a mortality rate of 91 per cent in an equal number of untreated controls. Augustine et al.<sup>37</sup> also using guinea pigs, found penicillin had no curative value after the appearance of clinical manifestations of the disease.

The action of penicillin on viruses and rickettsia is likewise not wholly clear. Heilman and Herrell<sup>38</sup> have reported that mice infected with the viruses of ornithosis and psittacosis can be protected by penicillin, whereas Aloragues, Pinkerton and Greiff<sup>39</sup> have shown that penicillin therapy reduces the mortality in mice infected with murine typhus fever. In both studies the dosage per kilogram of body weight was far in excess of that necessary in clinical practice to control infections caused by susceptible bacteria. To date no convincing reports have been published to indicate that penicillin is effective in any virus or rickettsial disease in man. When such infections are complicated by secondary infections due to organisms that are sensitive to the drug, the latter may be successfully treated with penicillin.<sup>40</sup> In contrast to the susceptible species, many important pathogenic bacteria are not adversely affected by the concentrations of penicillin that can be achieved in the blood and tissues (Table 2).

TABLE 2. *Organisms Not Susceptible to the Action of Penicillin.*

*Hæmophilus dactyli*  
*Eberthella typhosa*  
*Stizella dysenteriae*  
*Salmonella paratyphi*  
*Salmonella enteritidis*  
*Parvirella peris*  
*Vibrio cholerae*  
*Brucella melitensis*  
*Streptococcus faecalis*  
*Yersinia*  
*Molds*

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(To be concluded)

recovery. for one or more weeks after apparent clinical has usually been necessary to continue treatment gitis, bacterial endocarditis, and osteomyelitis, it similar period. In many infections, such as meningitis, signs of active infection have been absent for a normal for at least forty-eight hours or until the cillin has been given until the temperature has been treatment should be continued. In general, penicillin rules have been formulated concerning how long active infection may reappear. No hard and fast until the infection is eradicated or the signs of penicillin therapy, since the drug is bacteriostatic rather than bactericidal, treatment must be continued dosage is usually adequate.<sup>15</sup> It has been implied in discussing the action of penicillin that, depending on the size of the patient, from one half to one quarter of the adult

## CLINICAL ADMINISTRATION

A number of papers dealing with the general aspects of penicillin therapy have been published by several different groups of investigators.<sup>10, 14, 17, 18, 29, 55-60</sup> These reports describe the experiences of the various authors with a wide variety of infections. Although there have been differences in the details of treatment, the observations of the various groups are in general agreement. These papers will not be reviewed separately since it would appear more profitable, in discussing the clinical use of penicillin, to follow so far as it is possible an outline based on etiology. The views expressed in these articles will be reflected in the subsequent sections that deal with the treatment of specific infections. To avoid repetition, problems having to do with the site of the infection rather than the etiology of the process will be discussed first. At the end of the paper, recent work on the adaptation of penicillin to problems encountered in certain medical specialties will be considered.

*Local Factors*

In the section of the pharmacologic properties of penicillin, it has already been mentioned that it appears necessary in the treatment of bacterial meningitis to administer the drug intrathecally. The lumbar sac has been used by most investigators for this purpose, since the drug apparently diffuses from this site throughout the entire subarachnoid space in most cases. There appears to be no need, therefore, to introduce the drug into the cisterna magna or into the ventricles through burr holes, except in unusual circumstances. Twenty-four hours after a single intrathecal injection of penicillin a therapeutic level of the drug can usually be detected in the cerebrospinal fluid. Hence, one intrathecal injection a day is probably sufficient, although many workers prefer to give the drug every twelve hours for the first two to four days of treatment. Solutions containing 5000 to 10,000 units per cubic centimeter are usually employed, and with doses of 10,000 to 20,000 units no significant untoward effects have been observed. Until experience has shown that larger doses can be given with equal safety, it does not seem advisable to give more than 20,000 units in a single injection since this dose usually produces an adequate level of penicillin for at least twelve to twenty-four hours. Because the diffusion of penicillin through the subarachnoid space occasionally may be imperfect for one reason or another, it is strongly advisable, whenever the infecting organism is susceptible to the sulfonamides, to give full doses of an effective sulfonamide concomitantly with penicillin.

In the treatment of empyema the local instillation of penicillin is also recommended.<sup>28</sup> The irrigation of the cavity with physiologic saline solution after the aspiration of whatever pus or fluid

is present and before the introduction of penicillin is helpful. Intrapleural injections need be given only once every twenty-four to forty-eight hours, but a minimum of three injections is usually necessary to effect cure, and occasionally more prolonged treatment is required. Solutions containing 1000 units per cubic centimeter are usually employed, although the size of the cavity may make higher or lower concentrations desirable to ensure that the drug is brought into contact with all parts of the cavity.

In suppurative arthritis the local instillation of penicillin, whenever possible, is recommended. Although certain patients have responded to the systemic administration of the drug, this form of treatment is unreliable.

The treatment of bacterial endocarditis, regardless of the etiologic agent, requires prolonged therapy. Not infrequently the blood culture becomes negative after one or two days of treatment and the patient may show striking clinical improvement. Unless treatment is continued for at least two weeks, however, the chances of obtaining a lasting arrest of the infection are small.

The local use of penicillin without concomitant systemic administration in the treatment of soft-tissue wounds and superficial infections of the skin and subcutaneous tissues is occasionally effective.<sup>14</sup> When there is any significant area of cellulitis, however, the systemic administration of penicillin is usually necessary to obtain a maximum therapeutic effect. In selected cases, local penicillin therapy may often be combined with systemic therapy to good advantage. Penicillin is of no value when used as an irrigating solution, since it must remain in contact with infecting organisms for at least six to eight hours before it exerts its maximal antibacterial action.

*Dosage*

The problem of what constitutes an optimal dosage for the various infections treated with penicillin still requires extended investigation. It seems fairly clear that with the use of very large doses the results obtained are not superior to those following the use of moderate doses. Although excessive dosage has not been shown to be harmful to the patient, it constitutes a waste of a drug that is still not available in amounts sufficient to meet all the demands for its use. Once an effective bacteriostatic level of penicillin is achieved in the tissues, little seems to be gained by increasing the concentration in the tissues. Time is required for the natural defense mechanisms of the body to destroy the infecting organisms. It is doubtful whether this time can be shortened by increasing the dosage of penicillin excessively.

In most infections in adults, a dosage of 15,000 units given intramuscularly every three hours is usually effective. Exceptions to this rule will be



## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor\**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 31141

#### PRESENTATION OF CASE

A sixty-year-old laborer was admitted to the hospital because of dysphagia.

Sixteen months before admission the patient was unable to swallow solid foods for a period of one week. The food stuck in the lower esophagus and refused to pass into the stomach. This symptom disappeared and he had no more trouble until seven months before entry, when one morning he was unable to swallow his breakfast of oatmeal and prunes. The food was apparently arrested in the lower esophagus and had to be regurgitated, although on the previous day no difficulty whatever had been experienced. Since that time he had repeatedly tried to swallow solid and semisolid foods without success and had subsisted on a liquid diet. After the onset of this difficulty, the passage of food caused burning pain at the lower end of the esophagus. He had lost 12 pounds and had become weak and tired easily. He had never vomited blood or passed bloody or tarry stools. For the previous four years he had worked in a mill scouring wool. He had had a mild nonproductive cough in the evening for the past three or four months. For a year and a half he had had rather sharp nonradiating, precordial pain that came on during exertion and lasted a few minutes; this occurred one to several times a week. For six months he had had dyspnea on exertion and ankle edema.

Physical examination revealed a well-developed, fairly well-nourished, pale man. The skin was dry, and there was little subcutaneous fat. Many teeth were carious, with broken retained roots. The pharynx was moderately injected. Examination of the lungs was negative, no rales being heard. The heart was slightly enlarged to the left. A Grade 2 systolic murmur was heard over the apex and was transmitted over the entire precordium. The abdomen was negative. The ankles showed slight edema.

The temperature, pulse and respirations were normal. The blood pressure was 156 systolic, 62 diastolic.

Examination of the blood showed a red-cell count of 3,470,000 and a white-cell count of 5750, with

60 per cent neutrophils. The blood prothrombin time and the serum nonprotein nitrogen, chloride and protein levels were normal. The urine was negative.

X-ray examination of the teeth revealed retained, decayed root fragments surrounded by abscesses in the upper and lower jaws. X-ray films of the chest showed clear lungs, with no evidence of metastases or other abnormality. The heart was prominent in the region of the left ventricle, and the aorta was tortuous. The ribs showed no destruction. A barium swallow revealed normal function, the esophagus was dilated to a point 9 cm. above the diaphragm, at which level there was sudden and constant narrowing, with failure to distend and with absent peristalsis. An ulcer crater 6 mm. in diameter was present about 1 cm. below the top of the narrowing. Immediately below the narrowing, which extended for about 1 cm., there was dilatation to a maximum of 5.2 cm., which contracted readily and revealed what resembled gastric mucosa in a hiatus hernia (Fig. 1). The remainder of the stomach

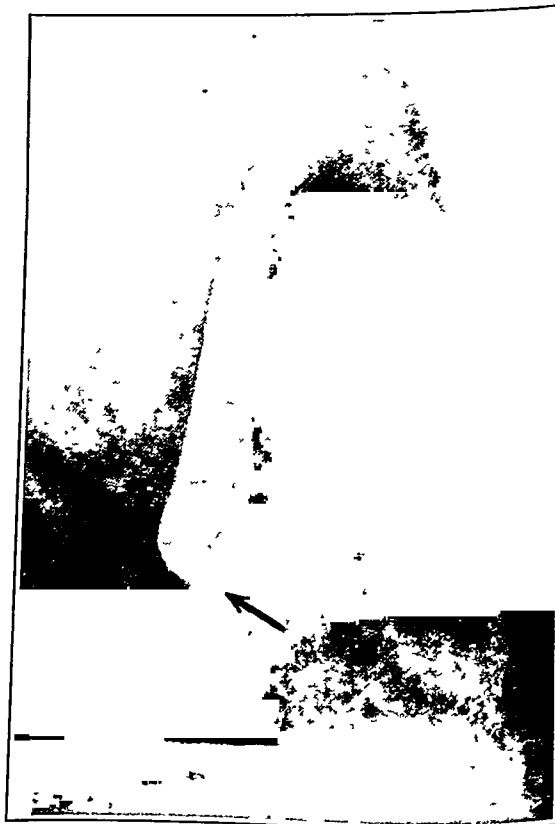


FIGURE 1. Roentgenogram Showing Obstruction in the Esophagus and the Herniated Portion of the Stomach Below It.

and duodenum was negative. The patient's teeth were extracted and he was given several transfusions.

One week after admission an esophagoscopy was performed.

calciated aortic knob, and a small amount of barium was delayed above this narrowing. Peristalsis of the esophagus was rather feeble. The narrowed area showed normal mucosal folds passing through it. There was no definite filling defect at any point. The lower two thirds of the esophagus showed rather marked curling. A 2-cm. hiatus hernia was noted, which emptied freely. The stomach and duodenum were normal.

On the fifth hospital day esophagoscopy was attempted. The esophagoscope was passed only to the level of the cricopharyngeus muscle, where there was prolonged delay. On gentle pressure some bleeding was noted in that region, and it was thought unwise to attempt to pass the instrument farther. The patient was given nothing by mouth. Intravenous sulfadiazine was started, and x-ray examinations of the neck and chest were performed on the following two days. No evidence of perforation of the esophagus was found. Following the esophagoscopy the temperature rose to 100°F. for a few days. The pulse and respirations remained normal.

On the eighteenth hospital day, as the patient was dressing to go home, she suddenly became dyspneic and cyanotic, broke out with a cold sweat and felt faint but had no pain. She had had no previous similar episode. The lungs were clear, the respiratory rate 30, and the pulse 160, with marked irregularity and pulse deficit. The blood pressure was 180 systolic, 60 diastolic. There was slight distention of the neck veins. She remained cyanotic and dyspneic, and a few hours later became comatose and expired.

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One must then consider the malignant lesions that might have been responsible for the clinical picture. Carcinoma of the esophagus may be excluded by the x-ray evidence of normal mucosal folds at the site of narrowing and the absence of a filling defect. Thus, it seems likely that the dysphagia arose from pressure on the esophagus by an extrinsic mass. There are no statements regarding this possibility in the x-ray report. Hence, it would be of help to

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DR. BENEDECT: I have seen several cases in which the inflammatory contraction was 10 to 15 cm. long. DR. SWEET: With a normally placed cardia? DR. BENEDECT: The cardia was not necessarily abnormally placed.

#### CASE 31142

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Ten years before entry she had a radical mastectomy for cancer of the right breast. Physical examination revealed a well-developed woman who showed evidence of recent weight loss. A right radical mastectomy scar was present; no axillary lymph nodes were felt. Examination of the heart, lungs and abdomen was negative.

The temperature, pulse and respirations were normal. The blood pressure was 154 systolic, 98 diastolic.

Examination of the blood showed a white-cell count of 6100, with 67 per cent neutrophils, and 14 gm. of hemoglobin. The urine was negative. The serum nonprotein nitrogen, the chloride and the protein were normal. A Hinton test was negative. An electrocardiogram suggested some coronary insufficiency.

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DR. RICHARD H. SWEET: I have been much interested in this group of cases, and we now have a small series characterized by the occurrence of a short-esophagus hiatus hernia and inflammatory stricture near the cardia, which in these cases lies well up in the chest.

At exploration in this man we found exactly what we see in the lateral roentgen-ray film, namely, a large portion of the stomach herniated through the diaphragm. The cardia and lower end of the esophagus were thickened. As in all such patients on whom I have operated the area was quite adherent. The adhesions in these cases are different from the ones that are encountered in carcinoma and somewhat more difficult to separate. I believed, as Dr. Wallace did, that this was a benign stricture arising as a result of ulcer in the cardia. This appears to be a definite syndrome. A co-existing duodenal ulcer has been observed in many of the cases. I agree with Dr. Wallace that these lesions should be regarded with suspicion and should be operated on unless it is obvious that they are suitable for dilatation. We have had cases with carcinoma arising apparently in the vicinity of such a stenosed ulcer. A short while ago I had a patient with a similar story, and at operation there was a firm, hard tumor mass, not much larger than 1.5 cm. in diameter, near the fibrous stricture. This led me to be radical in my resection. There was the same kind of stenosed cardia that would appear in a case of fibrosed stricture, but in addition there was a carcinoma, which apparently was extremely early. I know that Dr. Sniffen cannot say that this was a case of carcinoma arising in an ulcer, because of course that is difficult, even in the prepyloric ulcers. At least for the present I should like to think of these lesions in much the same way as we do those in the prepyloric area in the stomach and advise surgery rather than palliative therapy.

DR. BENEDICT: I might say that I have not seen any case with just this setup that had cancer except the one that Dr. Sweet mentioned. I should think that a number of them could be satisfactorily treated by esophagoscopy and dilatation. I am wondering if we ought to do such a radical procedure as partial resection for benign ulcer of the esophagus, except in rare cases.

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DR. SNIFFEN: One of the major stumbling blocks is that we cannot depend on the biopsy. Frequently, the sections show chronic inflammation and nothing more, and yet there is a cancer. In other words, the biopsy was not taken through a critical area.

#### CLINICAL DIAGNOSES

Stricture of esophagus, with ulceration and hiatus hernia.

Carcinoma of esophagus?

#### DR. WALLACE'S DIAGNOSIS

Benign ulcer of esophagus, with stricture.

#### ANATOMICAL DIAGNOSES

Short esophagus, with inflammatory stricture and ulceration.

Hiatus hernia.

#### PATHOLOGICAL DISCUSSION

DR. SNIFFEN: Dr. Sweet removed a little more than 2 cm. of the esophagus and a large portion of the part of the stomach that lay above the diaphragm. The upper end of the resected esophagus was dilated to 3.5 cm. in circumference. Below this there was an abrupt narrowing of the lumen, the wall being over 1 cm. in thickness. The stenosis extended for a centimeter or more, ending in the herniated portion of the stomach. In the stenotic area there was a small ulcer, which was not more than 2 mm. in diameter. Histologic sections showed a chronic inflammatory process, with ulceration in the squamous epithelium of the esophagus. There was nothing in the vicinity of the ulcer to lead one to think that there was peptic ulcer of an island of gastric mucosa in the esophagus. We know that these islands may occur anywhere in the esophagus.

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Stricture of esophagus, with ulceration and hiatus hernia.

Carcinoma of esophagus?

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Short esophagus, with inflammatory stricture and ulceration.

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X-ray examination of the esophagus showed that swallows of barium, both liquid and paste, passed through the esophagus with little delay. The esophagus was seen to be narrowed opposite a tortuous,

calcified aortic knob, and a small amount of barium was delayed above this narrowing. Peristalsis of the esophagus was rather feeble. The narrowed area showed normal mucosal folds passing through it. There was no definite filling defect at any point. The lower two thirds of the esophagus showed rather marked curling. A 2-cm. hiatus hernia was noted, which emptied freely. The stomach and duodenum were normal.

On the fifth hospital day esophagoscopy was attempted. The esophagoscope was passed only to the level of the cricopharyngeus muscle, where there was prolonged delay. On gentle pressure some bleeding was noted in that region, and it was thought unwise to attempt to pass the instrument farther. The patient was given nothing by mouth. Intravenous sulfadiazine was started, and x-ray examinations of the neck and chest were performed on the following two days. No evidence of perforation of the esophagus was found. Following the esophagoscopy the temperature rose to 100°F. for a few days. The pulse and respirations remained normal.

On the eighteenth hospital day, as the patient was dressing to go home, she suddenly became dyspneic and cyanotic, broke out with a cold sweat and felt faint but had no pain. She had had no previous similar episode. The lungs were clear, the respiratory rate 30, and the pulse 160, with marked irregularity and pulse deficit. The blood pressure was 180 systolic, 60 diastolic. There was slight distention of the neck veins. She remained cyanotic and dyspneic, and a few hours later became comatose and expired.

#### DIFFERENTIAL DIAGNOSIS

DR. IRA T. NATHANSON: The initial complaint of difficulty in swallowing focuses attention on lesions in or near the esophagus. Of the benign lesions, the Plummer-Vinson syndrome, scleroderma and vitamin deficiencies must be considered. The first can be ruled out by the absence of the usually long history of dysphagia, the age of the patient, the lack of x-ray evidence of webbing of the esophagus and the relatively normal hemoglobin. The visceral manifestations of scleroderma are less easily eliminated, because of the increased pulmonary markings and the sluggish peristalsis in the esophagus. In the absence of other clinical signs, both these findings may be attributed to the age of the patient. There are no findings recorded to suggest a vitamin deficiency.

One must then consider the malignant lesions that might have been responsible for the clinical picture. Carcinoma of the esophagus may be excluded by the x-ray evidence of normal mucosal folds at the site of narrowing and the absence of a filling defect. Thus, it seems likely that the dysphagia arose from pressure on the esophagus by an extrinsic mass. There are no statements regarding this possibility in the x-ray report. Hence, it would be of help to

review the x-ray films, particularly those of the chest, concerning which nothing is given in the abstract of the history.

DR. LAURENCE L. ROBBINS: The films of the chest show that the right breast had been removed. There appears to be an increase in the linear markings throughout the lung fields beyond what one can expect simply because of the patient's age. There is probably some increase in the density in the anterior portion of the chest; I am not certain what is the cause of this, although it might have been due to an acute process in the left upper lobe, as it appeared within twenty-four hours.

The spot films of the esophagus show it to be fairly smooth in outline; in the lower portion it appears to pass around an extrinsic mass. I do not believe that all the changes can be explained by curling.

DR. NATHANSON: Could the linear markings in the lungs be due to metastases?

DR. ROBBINS: They could be, but they are not typical. The changes could be on the basis of vascular congestion. There is a hiatus hernia.

DR. NATHANSON: If one assumes that an extrinsic mass was the cause of the symptoms, the question arises whether it was primary or secondary. The possibility of a primary mass in the posterior mediastinum cannot be definitely excluded, nor can the exact nature of such a mass be determined. A tumor of the lymphoma series, sarcoid or tuberculous lymph nodes may occur in this region. The latter two are relatively rare at this age, whereas the former may occur at any age. What is the probability of a secondary tumor? The patient had a radical mastectomy ten years previously for cancer of the breast. It is not known if the axillary lymph nodes were involved in disease. It is a well-established fact that metastases from cancer of the breast may remain dormant and not manifest themselves for many years, even twenty-five to thirty, after removal of the primary tumor. Good evidence exists that a five-year follow-up period is not sufficient to evaluate the curability rate of cancer of the breast. Moreover, metastatic lesions from cancer of the breast may appear in a wide variety of locations. The chest is a fairly frequent site. Thus it is possible that there was a metastatic mass in the posterior mediastinum that had its origin from the cancer of the breast removed many years before. Lesions of this character are not necessarily demonstrable by x-ray. There is no evidence of metastatic disease elsewhere. The evidence for this diagnosis is far from conclusive, but I cannot make any other from the material available.

Death can be explained on the basis of coronary disease or a pulmonary embolus.

## CLINICAL DIAGNOSIS

Carcinoma of esophagus.

## DR. NATHANSON'S DIAGNOSES

(Carcinoma of right breast.)  
Metastatic carcinoma of posterior mediastinum.  
Hiatus hernia.  
Hypertensive and arteriosclerotic heart disease.  
Coronary disease?  
Pulmonary embolism?

## ANATOMICAL DIAGNOSES

(Carcinoma of right breast.)  
Radical mastectomy, old.  
Metastatic adenocarcinoma of mediastinal lymph nodes, with compression and erosion of esophagus.  
Massive pulmonary embolism.  
Moderate bilateral hydrothorax.  
Fibrinous pericarditis.

## PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIFFEN: The patient died from a massive pulmonary embolus, and the inferior vena cava, as well as both femoral veins, contained large thrombi. In the right upper lobe there was a 5-by-3-cm. infarct of a few days' standing.

The mediastinal lymph nodes were matted together and enlarged by obvious tumor deposits. They surrounded the lower trachea and both main bronchi and on the left had produced stenosis of the left upper lobe bronchus, with partial collapse of the upper lobe as a consequence. The bronchial mucosa had been eroded by invading tumor at several points. Posteriorly these same lymph nodes had compressed a 6-cm. segment of the esophagus. The upper margin of compression was at the level of the aortic arch, and 4 cm. below this point the tumor had invaded the anterior wall of the esophagus and produced an erosion measuring 2 cm. in diameter in the mucosa. Additional findings were a moderate bilateral hydrothorax and a fibrinous pericarditis. No tumor could be found at the site of the previous mastectomy or in the other breast.

Microscopically the tumor in the lymph nodes was a poorly differentiated adenocarcinoma having a morphology quite consistent with a metastasis from a breast cancer. The cells lay in a dense collagenous stroma and had a rather striking proclivity for growth in the perineurial lymphatics. The vertebral bone marrow was the only site in which metastatic tumor could be found.

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## PENICILLIN: UNEXCELLED AND NOW OBTAINABLE

In a recent poll<sup>1</sup> of a group of leading physicians, penicillin was considered by the majority to be the most valuable drug now used by the medical profession. This recognition was based on two important properties of penicillin, namely, its wide range of effective action in bacterial infections and its lack of significant toxicity for man.

Until a year ago, penicillin could be aptly described as "unexcelled but unobtainable." During the past year the distribution of a limited supply of penicillin through depot hospitals has made it possible for an increasing number of physicians to

become familiar with its action from firsthand experience. On March 15 of this year the War Production Board announced that the production of penicillin had increased sufficiently to meet all the anticipated needs of both the armed services and the civilian population and that all restrictions on its sale had been removed. The solution of the difficult problems inherent in the large-scale production of penicillin is a notable accomplishment. Much credit is due the governmental agencies, private scientific institutions, and pharmaceutical manufacturers who have co-operated so effectively to achieve the goal of making the drug available to every patient who might benefit from its administration.

Although there is no reason to anticipate that the unrestricted distribution of penicillin will result in a shortage of the drug, it seems proper to urge physicians to employ this new therapeutic agent with wisdom and discretion. Elsewhere in this issue of the *Journal*<sup>2</sup> the present status of the use of penicillin in the treatment of infections is reviewed in detail. Physicians who have not had an opportunity to use the drug extensively will find this review helpful and timely in acquainting themselves with both the possibilities and limitations of penicillin therapy.

The wider use of penicillin should result in a significant lowering of the mortality rate, a decrease in the number of complications, and a shortening of the period of disability in many of the infections that are commonly encountered in medical practice. It is well to remember, however, that although the drug is nontoxic, it is not a panacea. In certain situations it is conceivable that if blind reliance were placed on the use of penicillin to the neglect of other therapeutic measures of known value, harm might result. Penicillin cannot be expected to have a favorable effect on diseases other than infections caused by organisms that are susceptible to its action, and even in such infections the use of adjuvant measures may often be necessary to effect recovery.

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## MEDICAL SERVICE IN INDUSTRY

EVERY vocational association strives to prevent the following of its trade or profession by unauthorized persons. This was begun by the medieval guilds and has been continued and amplified throughout the subsequent history of mankind. The primary purpose and the cause of its great success have always been the enhancement of the political power of its constituents, while they in turn contribute their aggregate strength to the power of the central organization. There is, however, a less well-known but more important purpose — that of protecting the mass of the people against fraudulent and unscrupulous exploitation. Medical-practice laws are framed to support the latter purpose, and it is the solemn obligation of those who make and enforce them to provide the people with a high standard of medical care. It is likewise the obligation of those who are admitted to practice within the law to keep the practice of medicine on a high plane and available to all people at all times.

What legally constitutes the practice of medicine may be a difficult matter to decide. In hospitals and institutions it is frequently necessary that the behavior of those who have to do with the sick and injured be codified into definite procedures. Such methods may be revised or amended from time to time to keep alive and maintain a complete understanding between all concerned. The ultimate responsibility for the choice and execution of the processes of medical care should be assumed by the doctor. In recognition of this responsibility the medical and nursing professions have long since adopted the principles of "doctor's orders"; doctors expect to issue them and to have them carried out, and nurses universally expect to receive them and to carry them out. They have worked well in hospital and private practice because in these surroundings the doctor is expected to assume command; indeed, hospital trustees generally require him to write his orders, where all may see and where there will never be any question about them.

In the development of modern concepts of industrial health, however, there have appeared new relations. Management as a whole cannot be ex-

pected to have the same interest or insight into medical care in industry that hospital administrators have in the medical care in their institutions. Industrialists naturally and properly utilize nurses and "first-aiders" to administer immediate aid and to carry out minor treatments. It has sometimes been thought that these nurses and first-aiders were not medically supervised. When, for example, does the giving of an aspirin tablet for a headache constitute medical practice, and when is it a minor commercial or friendly transaction? If the headache is due to meningitis, it is certainly medical practice to treat it in any way — from a first-aid medical cabinet, across a counter or in a hospital; but physicians cannot be expected to examine every case of headache on the remote chance that it may be a symptom of serious disease. Neither can they be expected to ignore everything of a minor nature. There are certain occupations in which headache may be a helpful sign of toxicity and may call for timely and expert medical attention.

All these perplexing and complex relations indicate the need for further clarification of the doctor's role in industry. The Council on Industrial Health of the American Medical Association has advocated standing orders for nurses in industry, and standing orders for industrial first-aiders have been privately issued and used. In its statement elsewhere in this issue of the *Journal*, the Committee on Industrial Health of the Massachusetts Medical Society expresses its approval of standing orders for industrial first-aiders, thus indicating its belief that the supervision of first-aid practices in industry is an obligation of the medical profession. It can be claimed that this is a device under which industrial first-aiders will "practice medicine without a license," and it probably would not be difficult to find cases in which such actually was the case. On the other hand, the practical view, and the one that the committee adopts, is that the first-aider will be less likely to practice medicine if he is forced to work under medical supervision expressed by written standing orders than if he is permitted to proceed independently. This may be a significant step in the protocol of industrial health.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON INDUSTRIAL HEALTH

The Committee on Industrial Health issues the following statement concerning industrial hygiene in Massachusetts.

DWIGHT O'HARA, *Chairman*

\* \* \*

#### A STATEMENT CONCERNING INDUSTRIAL HYGIENE IN THE SMALL PLANTS OF MASSACHUSETTS

In two previous reports to the Council of the Massachusetts Medical Society,<sup>1,2</sup> the Committee on Industrial Health has called attention to the fact that three quarters of the workers in Massachusetts are employed in the so-called "small plants" of the Commonwealth, factories where there is still little or no medical supervision of industrial hygiene. The committee has continued to discuss this fact and now ventures to issue a statement about it.

Many of these plants are not so small, — some of them employ 400 or 500 people, which is really a big industry, — but from the point of view of their health standards they are more comparable to the many little industries than they are to those large corporations that have found it feasible and profitable to maintain and staff their own medical departments. In the following discussion the term "small" is therefore used in the sense that it indicates small interest or activity in the field of industrial health.

It is easy to understand why these plants frequently lack this interest. Even though they aggregate a major industrial hazard to the people of Massachusetts, the management of each individual plant can actually concern itself with but a fraction of the total risk. It can insure itself against this fraction and let the matter rest right there. Of course, the chances are that this policy will keep it out of serious trouble, and management naturally is tempted to adopt it and turn its attention to other more pressing matters.

Although this is probably the attitude toward industrial health among many of the small industries, there are today an increasing number of them in which a lively interest in the subject is being shown. When the latter are looked at more closely, it is usually found that an enlightened manager has whipped a doctor into line or an enthusiastic doctor has applied the "bee" to management, or a restless nurse has refused to sink back into the routine of first-aid techniques; and so progress has been made. The development of part-time nursing services for industry by district nursing associations was commented on in the report of a year ago<sup>3</sup> and has been described elsewhere.<sup>4</sup> There are many plants in which no nursing service is used, but in which some sort of first-aid equipment has been installed. This is usually presided over by a certified "first-aider" or by someone in the plant who has come to take such responsibilities in the natural course of events. The committee desires to emphasize one point regarding all such persons, from the full-time nurse down to the casual first-aiders, namely, *they need medical supervision*. The complaint that is sometimes heard, or the fear that is sometimes expressed, that some of these people may be "practicing medicine" can mean only one thing — they are not properly supervised by the medical profession.

Such lack of supervision is generally due to one of three kinds of unwillingness: unwillingness on the part of management to employ a plant doctor; unwillingness on the part of the doctor to issue standing orders or to give any advance thought to the health hazards of the particular industry; or unwillingness on the part of first-aid or nursing personnel to refer cases to, or at least to secure advice from, the doctor. A lack of interest and of a sense of responsibility emanating from any one of these three points of view will be an effective barrier to improvement. Positive interest and enthusiasm from all three, on the other hand, will surely raise the standard of industrial health wherever it is applied.

A positive willingness on the part of management to employ a plant doctor must extend beyond the traditional readiness to consult the doctor after something has happened, which is mere medical care. Unless those concerned can look farther

ahead and establish standards of prevention and health, they are going to let many things reach the stage of requiring medical care that might well have been stopped in advance. Management should anticipate such things by analyzing its own risks, by utilizing engineering and medical knowledge to eliminate them or to place safeguards about them and by adopting a first-aid policy suitable to the needs of its particular plant. No first-aid policy is adequate if it has not had, in advance, complete medical approval. Management should expect to secure this and to pay for it, and the doctor should expect to provide it and to be paid for it.

A positive willingness on the part of the doctor to be called for purposes of inspection and observation of the conditions under which future patients may be injured, poisoned or exposed is most necessary. Too often — and especially now when all are overworked — the doctor does not believe that he needs to interest himself or to share in the development of such plant policies. He has many other responsibilities, and he naturally allows himself to be distracted by what, at any given moment, most urgently calls for his attention, but the standards of industrial health in the plant that employs him will never be high until he interests himself and assumes his share of the responsibility for the prevention of industrial disease.

The third type of unwillingness, that of the first-aid or nursing personnel to accept supervision of all their activities, is encountered only under special circumstances. Nurses are trained to work under medical supervision at all times, and first-aiders can be made to follow orders readily if the doctor insists on it. In some cases he has to insist on it, for the overconfident type of personality frequently and naturally establishes itself in first-aid positions, and may seek to exploit itself on that basis. It is, however, difficult to understand how any first-aider can overstep his assigned duties if he follows written standing orders from the doctor. On the other hand, when the doctor's interest is not sufficiently forceful, there may develop circumstances under which it may be legitimately charged that someone is practicing medicine without a license.

Chapter 149 of the General Laws of the Commonwealth of Massachusetts (Ter. Ed.), Section 141, states:

Every person operating a factory, shop or mechanical establishment where machinery is used for any manufacturing or other purpose except for elevators, or for heating or hoisting apparatus, shall keep and maintain, free of expense to the employees, such medical or surgical chest, or both, as shall be required by the department, containing plasters, bandages, absorbent cotton, gauze, and all other necessary medicines, instruments and appliances for the treatment of persons injured or taken ill upon the premises. Every person carrying on a mercantile establishment where twenty or more women or children are employed, shall in the manner aforesaid provide such medical and surgical chest as the department may require.

Under the provisions of this chapter the Department of Labor and Industries requires that a specific list of articles be kept and maintained in a clean and dustproof receptacle. Concerning the use of any of these articles the department provides the simple admonition, "WASH HANDS BEFORE USING." Surely the doctor can improve not only on this standing order but on the inventory of the first-aid kit required by the Department of Labor and Industries.<sup>4</sup>

Standing orders for nurses in industry have been endorsed by the Council on Industrial Health of the American Medical Association,<sup>5</sup> and at least one insurance company has compiled standing orders for industrial first-aiders.<sup>6</sup> The committee expresses its approval of such contacts between the practicing doctor and the industrial nurses and first-aiders. The nature and extent of the contact cannot be sharply delineated, for even in one industry, plants vary, managements vary, nurses vary, first-aiders vary and, above all, doctors vary in their concepts of what medical supervision is to consist. The written standing order, however, constitutes an authoritative level at which responsibility may rest. Although standing orders can often be only a general statement of principles, they are always subject to amendment, modification or alteration by the doctor in charge, and may conveniently provide him with an instrument wherewith he can assert his authority in an impersonal way.

The purpose of this statement is to indicate that progress in industrial health may be expected in the small plants of



Massachusetts by co-operative efforts on the part of managers, doctors, nurses and first-aiders. The absence of such co-operative effort, on the other hand, will effectually block any substantial improvement of the working conditions and environments. This statement is submitted for publication in the *Journal* in the hope that doctors who read it may better visualize their personal opportunities and responsibility in raising the standards of industrial health in the small plants of the Commonwealth.

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### DEATHS

**BENNETT** — William H. Bennett, M.D., of Norwell, died March 5. He was in his seventy-seventh year.

Dr. Bennett received his degree from Baltimore University School of Medicine in 1892. He was a fellow of the American Medical Association. He retired from active practice in 1938.

His widow, a daughter and a granddaughter survive.

**KELLEY** — Harry N. Kelley, M.D., of Worcester, died February 20. He was in his forty-sixth year.

Dr. Kelley received his degree from Harvard Medical School in 1925. He was on the staff at St. Vincent Hospital. He was a fellow of the American Medical Association.

His widow, a son, a daughter, a brother and two sisters survive.

**SANDERSON** — Robert Sanderson, M.D., formerly of Dedham, died February 21 in Arlington, Virginia. He was in his forty-second year.

Dr. Sanderson received his degree from Harvard Medical School in 1932. At the time of his death, he was a lieutenant in the medical corps and was stationed at the Navy Department in Washington. He was a fellow of the American Medical Association.

His widow and four children survive.

### CORRESPONDENCE

#### URGENT NEED FOR NAVAL MEDICAL OFFICERS

*To the Editor:* Because of the constantly increasing demand for naval medical officers, this office has been conducting a minute review of its files in the hope that physicians previously rejected might now be found eligible for a commission. It is therefore evident that for the first time a real opportunity exists for physicians who have been previously disqualified by either the Army or Navy. This action has been precipitated by a communication from Washington in which it was stated that the Bureau wished to review the applications of all doctors wherever there was a possible chance of acceptance. This review includes a large group of rejections based not only on questions of weight, height, color vision, and dental defects, but also such hitherto nonwaivable conditions as history of healed asymptomatic peptic ulcer, sacroiliac strain, history of asthma and several others. Although waivers will not be promised in such cases, the Bureau definitely wishes to scrutinize each individual case. It is the intention of this office to forward such requests to Washington for reconsideration accompanied by x-ray reports, laboratory data and any other pertinent information which will help to paint an accurate picture of the individual's current condition.

In addition, graduates of unapproved medical schools are encouraged to apply. While the professional examination is still a prerequisite, waivers for nonincapacitating physical defects may be granted to this group as well.

For men who have been declared *essential* by Procurement and Assignment, all we can say is that if a man *really wants to join the Navy*, he may appeal his classification with the assurance that his chances of being reclassified are, in most cases, excellent.

Contrary to public opinion, success in the field does not reduce the need for medical officers. Medical responsibilities mount in direct proportion to the number of victories in the field. The need is not an imaginary one — it rests on a definite factual basis.

This office is in possession of some interesting material that includes the most frequently asked questions regarding doctors and explains the various types of duties to which medical officers are assigned. Interested physicians may obtain copies on request.

H. S. GLIDDEN  
Commander MC, U.S.N.R.  
Senior Medical Officer

Office of Naval Officer Procurement  
150 Causeway Street  
Boston 14

### DEPRIVATION OF LICENSES

*To the Editor:* At a meeting of the Board of Registration in Medicine held February 21, the Board voted to revoke the license of Dr. Nathan Gaber, 129 Mt. Vernon Street, Boston, to practice medicine because of gross misconduct in the practice of his profession as shown by collusion.

H. QUIMBY GALLUPE, M.D., Secretary  
Board of Registration in Medicine

State House  
Boston

*To the Editor:* At a meeting of the Board of Registration in Medicine held March 16, after a re-hearing of the case of Dr. George J. Orlansky, now a captain in the Medical Corps of the Army and formerly of 1234 Blue Hill Avenue, Dorchester, the Board voted to revoke his license to practice medicine in this Commonwealth for not less than three years because of gross misconduct in the practice of his profession as shown by collusion.

H. QUIMBY GALLUPE, M.D., Secretary  
Board of Registration in Medicine

State House  
Boston

### NOTICES

#### HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of the Peter Bent Brigham Hospital on Tuesday, April 17, at 8:15 p.m. Brigadier Hugh Cairns, Nuffield Professor of Surgery, Oxford University, will speak on the subject "The Use of Penicillin in the Treatment of Pneumococcus Meningitis."

#### GREATER BOSTON MEDICAL SOCIETY

The next meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital, Boston, on Wednesday, April 18, at 8:15 p.m. Dr. Fuller Albright will speak on the subject "Osteomalacia." Discussion by Drs. Joseph Aub, Siegfried G. Thannhauser and Sidney Farber will follow.

#### SOUTH END MEDICAL CLUB

A regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, April 17, at twelve noon. Dr. William T. Salter, professor of pharmacology, Yale University School of Medicine, will speak on the topic "The Measurement and Adjustment of Endocrine Function."

Physicians are cordially invited to attend.

(Notices continued on page xvii)

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## TRENCH FOOT AND IMMERSION FOOT\*

CAPTAIN JAMES C. WHITE (MC), U.S.N.R., AND CAPTAIN WILLIAM B. SCOVILLE, M.C., A.U.S.

**F**ROSTBITE and kindred injuries to the feet from cold have been recorded as a source of casualties in military campaigns since the epic retreat of the Greeks under Xenophon across the snow-covered mountains of Armenia. Cold does not necessarily produce a single type of injury, as many have supposed, but may result in several distinct syndromes, which become of particular importance in time of war, when clothing, food, heat and shelter are likely to be inadequate and great numbers of indoor dwellers are exposed to the rigors of outdoor life. These clinical and pathologic changes have been summarized by Greene,<sup>1</sup> who has had an unusual opportunity to study them. Wet cold is far more difficult to deal with than are severer degrees of dry frost, as was found by Larrey<sup>2</sup> in the retreat of the Napoleonic armies from Moscow and by the medical officers on duty with the American troops who landed on Attu.

The two conditions to be considered herein, trench foot and its seagoing counterpart, immersion foot, are both caused by prolonged exposure of the dependent lower extremities to cold and moisture. The knowledge of trench foot as it is occurring during the present war is based largely on information acquired from Army surgeons who have taken care of many of the Aleutian casualties, in particular from Colonel R. H. Patterson and Major F. M. Anderson, of the Letterman General Hospital, and from Captain A. Lesser, with whom one of us (W.B.S.) was formerly associated at the McCaw General Hospital. Recently Captain M. H. Harris and Major G. L. Maltby,<sup>3</sup> of Ashford General Hospital, have presented a series of 130 cases resulting from the Italian campaign. These officers have been kind enough to contribute valuable criticism and advice, as well as to permit us to use much of their data for the compiling of this report. Since the writing of this article the War Department<sup>4</sup> has issued a comprehensive digest on trench foot.

Our information on immersion foot has been acquired largely through personal experience with

survivors of torpedoed vessels who have been exposed to cold water during a prolonged period adrift in the North Atlantic.<sup>5</sup> The opportunity to examine a large number of these men was obtained through the kindness of Surgeon Commander D. R. Webster, Surgeon Lieutenant F. M. Woolhouse and Surgeon Lieutenant J. L. Johnston, of the Royal Canadian Navy. Others have been examined at the Columbia-Presbyterian Medical Center in New York through the courtesy of Dr. David C. Bull and at the Massachusetts General Hospital, in addition to those cared for at the United States Naval Hospital in Chelsea.

### PATHOLOGIC PHYSIOLOGY

In a crowded lifeboat or Carley raft the survivors are forced to sit with their wet feet dependent and immobile. This alone is sufficient to produce edema, and if starvation is an added factor, so that the plasma proteins are reduced, the edema becomes pronounced even in the absence of cold. No lifeboat or raft is dry, and boots are not issued that will keep the feet both dry and warm. Occasionally when a man has been forced to kneel for prolonged periods on the floorboards of a wet boat or to sit on the bottom of a rubber raft, the same condition has involved the knees or the buttocks.

In the landings in the Aleutians men were forced to take cover in foxholes in a semisitting position for periods ranging from three to fourteen days, in melting snow by day and in light frosts at night. During this period they had little to eat, were thoroughly chilled and had no opportunity to change their footgear. No leather boots can keep out the wet under these conditions, and even rubber ones become moist on the inside from perspiration. Under these circumstances all the factors that damage the tissues in a crowded lifeboat in the North Atlantic are present ashore—exposure of the legs to cold just above freezing, wetness, dependency and immobility, and general chilling of the body.

Immersion foot and trench foot differ from frostbite simply because the tissues are not actually

\*This article has been released for publication by the Division of Publications, Bureau of Medicine and Surgery, United States Navy. The opinions and views set forth are those of the writers, and are not to be construed as reflecting the policies of the Navy Department.  
Presented at the annual meeting of the New England Surgical Society, Boston, September 20, 1944.

frozen. Ice crystals do not form in living tissue above the freezing point of sea water or of mud and thawing snow, but at temperatures from this point to above 50°F. the feet gradually become chilled,

crowded lifeboat do not have the opportunity to walk and thus to traumatize their anesthetic feet. When this occurs, infection is likely to follow and to end in moist gangrene. After the recent campaign in the Aleutians, 6 cases of a total of 231 treated by Patterson and Anderson<sup>9</sup> required amputation of one or both feet, and 18 other patients lost the greater part of one or more toes. At the McCaw General Hospital, 21 of 35 severe cases from Attu required late plastic amputation revisions of toes or distal portions of the feet by Captain Lesser.

After exposure at sea, infection and gangrene are fortunately less frequent than is the case on land. In approximately 100 cases that we have seen, only 1 man lost his leg, — after exposure for a prolonged period adrift in bitter cold off the northern tip of Norway in January, — and 2 others suffered the loss of one or more toes. After comparing our observations of trench foot with those of immersion foot,



FIGURE 1. *A Case of Immersion Foot.*

These photographs were taken of a patient of Surgeon Commander Webster, R C N.M.C., on the twelfth day after rescue. The man had been in a lifeboat without shoes for four days in the North Atlantic in March. The temperature of the sea water was recorded at 34°F, and his feet had been wet most of the time. The petechial hemorrhages and subcutaneous swelling are well shown. Blisters were present, but shrank following cooling to 70°F. with ice bags. There was threatened gangrene of the third and fifth toes on the left and the second, third, and fifth toes on the right, which eventually necessitated local amputation of several after infection, which entered through areas of epidermophytosis.

numb and swollen (Lewis<sup>6</sup>). Lesions resembling trench foot have been reproduced in rabbits by shaving the legs and keeping the animals standing for a number of days in a refrigerated chamber on wet mud at a few degrees above freezing (Smith, Ritchie and Dawson<sup>7</sup>). Tissue changes similar to those seen in immersion foot have recently been produced experimentally by Blackwood and Russell<sup>8</sup> in the tails of rats by keeping the floors of the cages wet with sea water at 40°F. for periods of two to four days. In sailors adrift at sea these changes may begin in the course of a few hours, but in the trenches, where the feet get wet and chilled more slowly, an exposure of several days is necessary. The condition at sea differs from that seen in troops campaigning in slush and cold mud simply because men in a



FIGURE 2. *A Severe Case of Trench Foot from Attu*

In this case, amputation of both feet was eventually necessary because of the depth of tissue necrosis and because gas bacilli were found on smear and culture. (Reproduced by courtesy of Col R H Patterson and Maj F M Anderson, M C, A U S, Letterman General Hospital)

it is our impression that the former causes more extensive and severe damage to the tissues than does the latter.

When first seen after exposure, either ashore or afloat, the feet are cadaveric in color, swollen and

blistered (Fig. 1). Massive gangrene from the ankle down may appear imminent (Fig. 2), but in the absence of infection and with proper treatment the capacity for recovery is amazing. It takes place in two stages, an early hyperemic stage and a later period of fibrosis. If the exposure has been severe and prolonged, pain may be severe in both and may cause prolonged incapacity.

The hyperemic phase develops as soon as the legs become warm and circulation recovers. This vasodilator response is a sterile inflammatory reaction

blistering, as well as the late fibrosis (Drinker and Field<sup>11</sup>). The combination of heat, which raises the metabolic demands of the cells for oxygen, and of an inadequate superficial circulation results in cutaneous anoxia and burning pain as soon as the nerves recover (White<sup>8</sup>). Recovery of sensation takes place rapidly over the proximal parts of the feet, but in the severer cases the toes may remain anesthetic for weeks.

In the course of one to four weeks the hyperemia subsides and the circulation returns to normal.

Moderate hyperemia and anesthesia, without much cutaneous injury, 2 weeks after rescue.

Appearance of feet: Redness of skin and petechial hemorrhages.

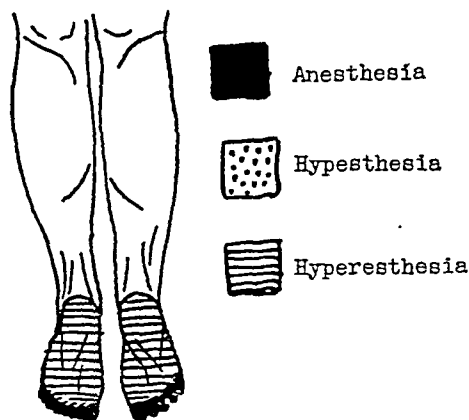
Redness most striking in dependency. Very slight residual swelling. Superficial loss of epithelium on soles.

Arteries: All pulsations strong.

Veins: Very prominent.

Sweating: Began slightly over skin of proximal feet at 13 days.

Neuritis: +++, beginning to subside.



#### Sensation

Touch, vibration, and detection of figures present except in toes.

Two-point discrimination slightly reduced over dorsum of feet, absent in toes.

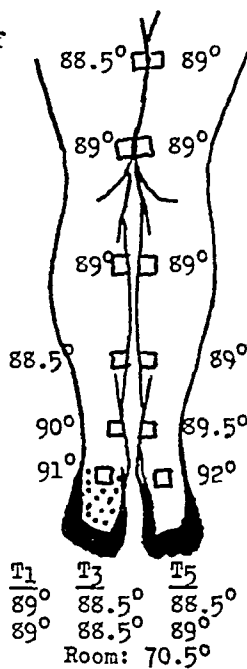


FIGURE 3. Sensory Changes and Surface Temperatures in a Case of Immersion Foot.

caused by the absorption of damaged tissue. There are bounding pulsations in the deep vessels, and heat, radiating to the surface, makes the skin fever-hot (Fig. 3). In addition, the circulation of the superficial tissues, which have been more thoroughly penetrated by the cold, may be profoundly impaired. Evidences of this are the petechial hemorrhages caused by ruptured capillaries and the thrombosis of the subcutaneous blood vessels (described by Patterson<sup>10</sup>). Capillary permeability is greatly increased, resulting in the extravasation of protein-rich fluid that cannot be removed by the injured lymphatics. This accounts for the gross edema and

The blebs absorb and the skin peels off with a certain amount of scarring. The patients with milder cases are then fit to return to duty, but in those with severer damage the skin is atrophic (Fig. 4), movement of the toes is limited (Fig. 5), and walking is made difficult by pain. No satisfactory explanation for the rigid, weak feet and pain on walking had been given until the past winter. Dr. Shields Warren and one of us (J.C.W.)<sup>12</sup> examined a series of biopsies of skin and superficial muscle from the feet of 6 men who were still incapacitated several months after their exposure. These biopsies showed atrophy and thinning of the epidermis, with intense fibrosis and

deposition of collagen around the nerve endings and subcutaneous blood vessels (Fig. 6). The muscles were also infiltrated and their fibrils separated by

that, in addition to the widespread fibrosis, other contributory factors in this prolonged period of disability are the weakness and deformities of the feet secondary to their long-continued immobilization and the hyperesthesia that frequently ac-



FIGURE 4. *A Late Case of Trench Foot After Conservative Local Amputation and Healing.*

*This photograph illustrates the cutaneous fibrosis, the severe contractures and the rigidity of the toes. (Reproduced by courtesy of Captain Albert Lesser, McCaw General Hospital.)*

a network of scar tissue (Fig. 7). The extent of this reaction depends on the initial exudation of fibrin and tissue anoxia. It is the logical explanation for the late pain, rigidity and weakness of the feet, a condition that tends to improve spontaneously in six to eight months, the time at which collagen ceases to contract. In some of the worst cases of immersion foot on record, however, pain has remained troublesome for over two years (Ungley<sup>13</sup>).

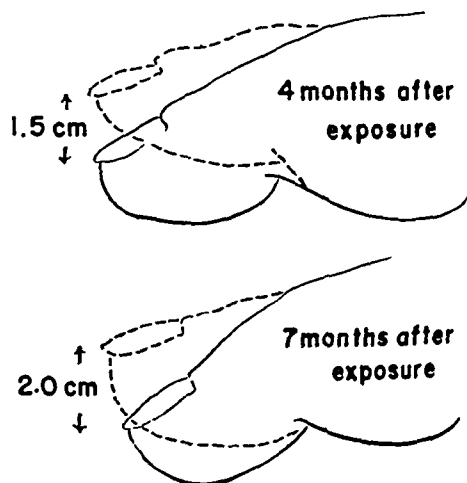


FIGURE 5. *A Late Case of Immersion Foot*

*This photograph illustrates the rigidity and limited movement of the toes. Note the improved mobility after three months of orthopedic exercises and physiotherapy. (Reprinted from White and Warren<sup>12</sup> by permission of the publisher.)*

companies the return of sensation after nerve injury in any part of the body.

A final point to remember in the pathogenesis of these swollen, painful feet after prolonged periods

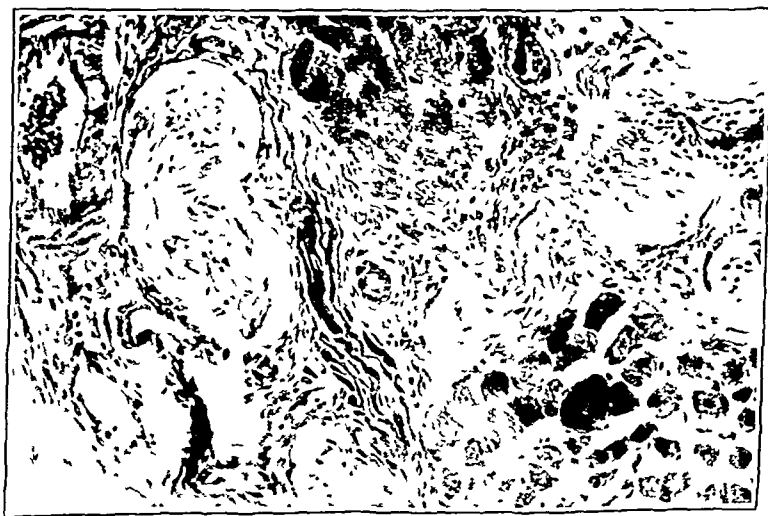


FIGURE 6. *Photomicrograph of a Section of the Extensor Brevis Digitorum Muscle. Note the perineural fibrous tissue and the edema of the nerves (x 220; Masson trichrome stain). (Reprinted from White and Warren<sup>12</sup> by permission of the publisher.)*

After seven months even the patients with mild cases of trench foot from Attu were for the most part still unable to march on account of hypersensitive feet. Patterson and Anderson<sup>9</sup> have suggested

of cold and wet is the role of malnutrition and avitaminosis. One of us (J.C.W.<sup>14</sup>) has seen extreme swelling, numbness and pain develop after two weeks of dehydration and starvation with exposure in the

warm waters of the Gulf Stream. These conditions were caused not by tissue injury from cold but by hypoproteinemia and avitaminosis—particularly through depletion of the vitamin B complex. Similar conditions are even likelier to be found in the starving inhabitants of Europe and Asia.

#### TREATMENT

When men with chilled, numb, swollen and blistered lower legs are first seen by a medical officer, they must be kept off their feet and the skin protected against rupture of the blebs and the formation of pressure sores in the weight-bearing areas of anesthetic skin. Once streptococcal infection has begun, moist gangrene and loss of the leg are

directing a blast of air from an electric fan or blower over them. The feet should never be rubbed or the blistered areas painted with a strong disinfectant. Like a second-degree burn, these areas should be handled with aseptic precautions, including masking of the dresser's nose and mouth, sulfonamide therapy and a "booster dose" of tetanus toxoid. Elevating and cooling the legs helps to drain the edema fluid and causes the blisters to shrink. During the period of sterile inflammation the hyperemia of the deeper tissues, which are always less damaged by cold than is the skin, causes the surface temperature to rise to above 90°F. Unless this excessive heat is reduced, cyanosis increases, blisters swell, and pain becomes acute. The explanation of this is that



FIGURE 7. Photomicrograph of a Section of the Extensor Brevis Digitorum Muscle. Note the fibrous tissue about nerves and between the muscle bundles ( $\times 35$ ; phosphotungstic acid-hematoxylin stain). (Reprinted from White and Warren<sup>12</sup> by permission of the publisher.)

likely to follow. First aid should therefore be begun by having the patients carried to the sick bay or hospital near the front lines and kept in bed.

Entirely different forms of treatment are required for the general effects of cold and the local damage from exposure. The body should be warmed externally by covering with blankets and hot-water bottles, and internally by drinking hot soup, coffee or tea. The patients should be given nutritious, easily digested food with a high protein-vitamin content as soon as it can be tolerated. In the sickest survivors, vitality may have been so reduced by cold and starvation that emergency treatment for shock is needed. Transfusion of plasma then plays a double role by restoring depleted fluid volume and combating hypoproteinemia.

It is vitally important to keep the injured feet of the chilled patient cool while the body is warmed. This is best accomplished by exposing the legs below the knees to a cool room temperature and

warming increases the metabolic demand for oxygen on the part of the cutaneous cells to a greater extent than can be met by the impaired supply of blood through the injured subcutaneous vessels. Anoxia therefore ensues, with throbbing pain, increased extravasation of fluid and necrosis of the skin.

After arrival in a naval or Army base hospital the same local treatment should be continued for a week or more, until the hyperemia due to absorption of damaged tissue has subsided and circulation through the thrombosed subcutaneous vascular bed has recovered. The greatest advance in the treatment of the acute hyperemic stage has been the application of continuous cooling by Webster, Woolhouse and Johnston.<sup>15</sup> In general, local cooling should be pushed to the point where pain is relieved. The ideal cutaneous temperature level is between 75 and 70°F. This has been established by Safford and Nathanson<sup>16</sup> both by clinical observation and on theoretical grounds. Cooling lowers the metabolic

need for oxygen to a point at which sufficient quantities can be supplied through the injured capillary bed. When the feet are cooled the appearance of the skin improves, blisters shrink, and pain is relieved. In the severest cases cooling with room air is insufficient and treatment with ice bags may be necessary. When the latter are used, sterile pledgets of cotton are placed between the toes and the whole foot is covered with a sterile towel. Thoroughly dried ice bags are then placed around each foot over the towel, and the whole is encased in an oiled-silk bag, around which in turn are wrapped thick layers of cotton waste or other insulating material. A rubber pillowcase, loosely tied below the knee, forms a satisfactory outer covering. At first, two to four ice bags are necessary to cool the foot to the optimum temperature of 75 to 70°F. Ordinarily it is sufficient to change them every four hours, and at these times the toes should be palpated to make sure that they are not too severely chilled. It may be necessary to carry out this treatment for periods ranging from several days to two weeks, but as hyperemia subsides less ice is required, and finally exposure to cool air alone suffices.

In the rare cases in which edema and blistering are pronounced but pain is so slight that cooling of the skin is not vital, compressive dressings, which are so effective in second-degree burns, deserve a trial. This has been suggested to us by Dr. Sumner L. Koch,<sup>17</sup> but to date no suitable case has been found for trial.

When gangrene has already developed before the patient enters the hospital, periodic débridement and painstaking care of the feet are necessary. In most cases the extremities can be saved, at least in part, by conservative amputation of toes and the distal portions of the feet (Fig. 8). Early amputation of a leg is excusable only in fulminating lymphangitis, threatened septicemia or gas gangrene.

When the products of tissue damage have been absorbed, circulation returns to normal, blebs absorb, and the skin desquamates. In the mildest cases the patients may be fit to return to duty within two weeks, but severe disability may last for months. All severe cases of trench and immersion foot run a prolonged convalescence of six or more months because of interstitial scarring and pain. The scarring results in rigidity and contractures of the toes, as well as atrophy and weakness of the ligaments and intrinsic muscles of the feet. The pain is of two varieties — a burning, hyperesthetic type, probably due to irritation of nerve endings by scar tissue, and a dull ache in the arches and ankle joints, probably due to a combination of muscle weakness, disuse, rigidity and fallen arches. Physiotherapy and orthopedic exercises are helpful in restoring power to the intrinsic muscles and weakened arches, but often fail to give sufficient relief.

A vast saving in man power for the Army, Navy and Merchant Marine can be achieved if a method

is found to shorten this period of pain and rigidity. Although sympathectomy is quite illogical in the early hyperemic stage, it is possible that release of vasoconstrictor tone will reduce these late disabling



FIGURE 8. *The Results of Conservative Treatment of Gangrene in a Case of Trench Foot (Reproduced by courtesy of Col. R. H. Patterson and Maj. F. M. Anderson, M C, A U.S., Letterman General Hospital)*

symptoms by hastening the absorption of collagen and fibrous tissue and by increasing the superficial and collateral circulation through the injured extremities. This operation should therefore be seriously considered in selected cases and warrants extensive trial and critical observation. Although Harris and Maltby<sup>3</sup> have been impressed by the frequent association with vasospasm, this has in our experience been the exception rather than the rule. Only 3 of 36 soldiers with severe trench foot from Attu and 2 sailors had this complication to a well-marked extent. All were dramatically improved by sympathectomy (Fig. 9). In addition, a limited number of cases with atrophic, rigid feet, as well as certain cases of delayed wound healing

that did not exhibit vasospasm, have been treated by lumbar sympathetic ganglionectomy. The results to date have been gratifying. It is therefore proposed that unilateral sympathectomy be tried in a representative series of cases of bilateral severe trench feet exhibiting atrophy, rigidity and fibrosis. For completeness the series should include cases both with and without vasospasm.\* At the time of operation a biopsy, to include a bit of skin, sub-



FIGURE 9. A Case of Immersion Foot Eleven Months after Exposure.

This photograph shows fibrosis and an indolent ulcer of the big toe. These feet were cyanotic, cool and sweaty, but the arterial pulsations were maintained. There was a good response to paravertebral procaine block and to lumbar sympathectomy, which was followed by vasodilatation, healing of the ulcer and relief from the aching pain.

cutaneous tissue and extensor brevis digitorum muscle, should be obtained from the dorsolateral aspect of each foot.<sup>12</sup> This biopsy should be repeated three months postoperatively so that the effects of sympathectomy can be finally and accurately assessed by comparing the tissues from sympathectomized and nonsympathectomized feet.

Before closing, a word of caution must be interjected. In seeing a large number of late initially mild cases of trench feet, one of us (W.B.S.) has become impressed with the susceptibility of such cases to an hysterical prolongation of symptoms and disability, and with the need for correction of purely mechanical dysfunctions secondary to prolonged disuse, muscle weakness and contractures. Arch supports and both orthopedic and psychiatric evaluation are imperative. In the severe cases every effort should be made to avoid early radical amputation. As in frostbite, delayed amputations result in the loss of only a few toes or the distal portion of a foot, and almost never the loss of an entire foot. This was demonstrated conclusively by Captain Lesser at the McCaw General Hospital in the cases of trench foot evacuated from Attu (Fig. 4).

\*Cases with vasospasm are intended to include all patients with cold, cyanotic feet with or without excessive sweating that respond effectively to diagnostic procaine block (White<sup>13</sup>).

In conclusion, the lesions of trench and immersion foot can frequently be prevented by prophylactic measures of foot hygiene in troops campaigning under winter conditions and by safety measures at sea. Early emergency treatment largely determines how much of the foot and toes can be saved and how long the disability will continue. Late forms of therapy should include orthopedic and psychiatric measures, as well as sympathectomy in selected cases. Future efforts to improve the handling of these conditions should include further studies on the effects of climate and protection from exposure, widespread instruction in foot care and first aid and critical evaluation of the effect of sympathectomy on the absorption of fibrous tissue and collagen, as well as on the relief of pain.

### SUMMARY

Trench foot and immersion foot are similar clinical entities that differ from frostbite in the type of exposure and the reaction of the tissues and their method of recovery.

Three stages in the course of these syndromes are described: the initial response to cold short of actual freezing of the tissue cells, the early period of recovery, characterized by painful hyperemia, and the residual effects of fibrosis.

Initial treatment is similar to that for burns, but should include cooling to reduce the oxygen demands of the skin to a level compatible with the flow of blood through damaged subcutaneous vessels.

Late treatment consists of conservative minimal amputations, exercises and physiotherapy to decrease tissue fibrosis and joint stiffness and sympathectomy in selected cases with residual circulatory insufficiency.

Gangrene of the toes and distal portions of the feet constitutes a serious problem in trench foot, but is rare in immersion foot, in which the lower extremities are less liable to trauma and infection.

Prolonged partial disability is frequent in both conditions.

Orthopedic and psychiatric factors must be taken into consideration.

Improvement in protective clothing, widespread instruction in foot care and first aid and a critical evaluation of the response of the fibrosed tissues to sympathectomy are in order.

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## DISCUSSION

DR. EUGENE E. O'NEIL, Boston: These cases of trench foot and immersion foot, I dare say are not very much unlike those of trench foot that occurred in the last war, several of which I saw. I have seen a few of the present cases at the United States Marine Hospital, and all of them appeared to have taken on the rather late phase that Dr. White has emphasized; that is, they showed marked vasomotor disturbances — so marked, as a matter of fact, that they had all the earmarks of well-advanced Buerger's disease. When subjected to lumbar sympathectomy, as was done if the operation was indicated and if their collateral potential appeared sufficient to be developed in this manner, these patients improved almost without exception.

It occurred to me that, in view of what Dr. White has said about the hyperemic stage of immersion foot, it might be well to inquire from some of these sympathectomized patients what had happened shortly after the trench foot developed. Two of them stated that for two or three weeks following the onset they went through what was apparently a hyperemic stage. The feet were swollen and blistered and were extremely hot. Seeing these cases in the acute stage, one would think that they had been sympathectomized, but as time went on they have taken on the peculiar picture of progressive vasomotor disturbance and have been improved by sympathectomy.

CAPTAIN WILLIAM B. SCOVILLE: Within the Army, trench foot constitutes a most serious disability, far more serious than it is in civilian life. Rarely do any but the mildest cases return to combat duty, and hospitalization generally exceeds six months. This is because the disability prevents marching and standing, especially in inclement weather. I am told that the Russians consider these casualties of so serious a nature that they have gone to extraordinary and unique prophylactic lengths to prevent their recurrence. In their usual definitive fashion, they assign each soldier going to a cold climate to a companion, each man acting as the guardian of the other's feet. If one soldier gets a blister or frostbite, both soldiers are held responsible and both are liable to be shot — so the story goes. By this method, solicitude over one another's feet was simply intense.

In the northwest United States I saw severe cases of trench foot resulting from the Attu campaign. Thirty-five cases were followed by Captain Albert Lesser. All were gangrenous or near gangrenous, and 60 per cent required late conservative amputations of toes or portions of the feet. Even in such severe cases, only 3 showed evidence of vasospasm. From this small series, I concluded that constitutional autonomic instability with vasospasm is not a predisposing cause of trench-foot. This has been borne out by Captain White's studies. On the other hand, I was impressed by the extreme prevalence of vasospastic disease in soldiers stationed in the

cold climates of the Alaskan and Northwest theaters. A great number of these cases occurred in soldiers who had spent their entire life in warm climates. Although vasospasm is rare in trench and immersion foot, sympathectomy may have some place in hastening the reabsorption of scar tissue and collagen — common sequelae in trench foot, as shown by Captain White and Dr. Warren. Only further research can settle this point. Small subcutaneous biopsies taken from both feet before and after a unilateral sympathectomy should give the clue.

My studies on sympathectomized cases of trench foot first whetted my interest in the effects of sympathectomy on the treatment of chronic indolent wounds and infections of the feet. The results of such a procedure in these cases have been most gratifying, so much so that we now recommend it in the majority of cases that have failed to heal within six months' time regardless of the presence of vasospasm. I have in mind several such cases, and mention a case of osteomyelitis of the great toe following a gunshot wound that had drained continuously for eight months, with removal of sequestrum two months previously. Pain and drainage had continued. Nine days after sympathectomy drainage stopped and the pain was immediately and progressively ameliorated. In another case, an indolent low-grade infection in the nail beds of both great toes followed recurrent attempts at removal of the matrix of ingrowing toenails by an overzealous young medical officer who had used every known method to kill the matrix of the nail, including scalding the nail bed with hot fluids. When seen by us, this patient had not put either foot to the ground for over a year because of pain and still had unhealed granulations in the nail beds. Unilateral sympathectomy with the other foot used as a control gave most gratifying results in healing and epithelialization, as well as in subsidence of the pain.

I offer two final words of caution concerning the therapy of trench foot. The first is a plea for extreme conservatism in amputation. In Lesser's series of severe cases, the majority of surgeons who saw such cases on their admission to Army hospitals cheerily advised, "You may as well amputate now as later," but after four to six weeks of conservative and meticulous care the healing of apparently hopelessly ulcerated toes and feet was startling. The second word of caution lies in the psychiatric field. Trench foot is closely akin to low-back pain in its predisposition toward neurosis. The drama of onset, the vagueness of the pain and the absence of objective disease in the mild cases all make it easy for these patients to capitalize on their disability. When patients continue to complain of pain for periods of longer than six months without objective evidence of peripheral vascular disease or tissue damage, a neurosis should be suspected.

DR. JAMES C. WHITE, Boston: The term "Raynaud's disease" has been loosely used here. It should be qualified so as to indicate cold, clammy, cyanotic feet that show a dramatic improvement in circulation following procaine block or lumbar sympathetic ganglionectomy. I do not believe that these men who have been exposed to cold and moisture have actual blanching of the toes, as I have not yet seen one with this condition. They do have continuous excessive vasoconstriction, with a tendency to excessive perspiration in the extremities.

Another question of interest is why this phenomenon is so frequent. Many people have a tendency to cold, moist hands and feet, and this is often greatly increased after emotional stress. Dr. Frank Fremont-Smith and Dr. Stanley Cobb discovered a few cases of typical Raynaud's disease in which the first bouts of phasic asphyxia developed on the breaking off of an engagement, the death of a husband, financial failure or some other cause of severe emotional disturbance. These men whom we have been discussing have, of course, been through an extremely severe emotional disturbance. If they go on having incapacitating pain and are banded about in service hospitals and their compensation is not adjusted, they have every reason to develop chronic vasospasm in their feet.

## MEDICAL PROGRESS

## THE TREATMENT OF INFECTIONS WITH PENICILLIN (Concluded)\*

DONALD G. ANDERSON, M.D.†

BOSTON

*Staphylococcal Infections*

Penicillin has proved to be the most effective chemotherapeutic agent yet discovered for the treatment of staphylococcal infections.<sup>55, 56, 62</sup> The usual mortality rate of 80 per cent in untreated cases of staphylococcal bacteremia<sup>63</sup> has been reduced with penicillin treatment to 20 per cent or even less. Doses between 150,000 and 300,000 units a day are usually desirable until the infection has been controlled. The daily dosage may then be reduced to 120,000 units. It has been widely recognized that in severe staphylococcal infections striking improvement may not be observed for several days after the beginning of treatment. It is not unusual, however, for the patient to begin to look and feel better several days before the temperature returns to normal. Not infrequently the blood culture may still be positive when the first signs of improvement are noticed. The rapidity of the response to treatment, as well as the end results, are influenced by several factors, including the severity of the primary lesion, the number of metastatic lesions, the accessibility of both primary and secondary foci to surgical drainage and the general condition of the patient. The poorest results are obtained when the infection localizes on the endocardium, giving rise to a bacterial endocarditis. Even this complication, however, occasionally responds to treatment with penicillin.

Although surgical drainage is frequently an important adjunct to penicillin in the treatment of staphylococcal bacteremia, there are certain infections in which, not infrequently, the withholding of operative measures may shorten the recovery period and result in less permanent dysfunction or disfigurement. Since carbuncles, for example, respond very well to penicillin treatment, surgical intervention, except for the evacuation of obvious collections of undrained pus, no longer seems to be necessary. Treatment for ten to fourteen days has usually effected complete resolution of the infection, although the separation of slough and the epithelialization of denuded areas often has not been complete for another one to three weeks.

Acute hematogenous osteomyelitis appears to be best treated without surgical drainage, except in the presence of a large soft-tissue abscess. Under penicillin treatment alone the rapidity of clinical recovery and the extent of healing and repair of the bone appear to surpass that of cases treated with surgical drainage.<sup>64</sup> An exception to this statement must be made for those cases in which a suppurative arthritis is also present. In such patients there is a great possibility that the joint will be destroyed unless penicillin can be introduced directly into the joint space. When a suppurative arthritis is present, it seems advisable to perform early whatever surgery is necessary to facilitate the local instillation of penicillin into the involved joint once or twice a day. It has been desirable in acute osteomyelitis to continue treatment for at least two or three weeks, and in severe cases with multiple lesions longer treatment has been necessary. Since the roentgenographic changes in the bone do not keep pace with the clinical progress in this disease,<sup>14, 64</sup> reliance has had to be placed on the clinical signs of recovery in determining when to stop treatment. Not infrequently the destruction of bone has been most extensive at a time when it was obvious clinically that the patient had recovered. Even though treatment was stopped at this point, rapid repair of bone with a striking return toward a normal bone architecture usually took place in the next few weeks or months. In occasional cases that were treated extremely early, no signs of bone destruction developed in the roentgenograms.

Kirby and Hepp<sup>65</sup> have reported excellent results with penicillin therapy in the treatment of osteomyelitis of the facial bones. When sequestrums were present, surgical treatment in addition to the use of penicillin was necessary to effect complete recovery.

Anderson, Howard and Rammelkamp,<sup>43</sup> in a study of the management of chronic hematogenous and traumatic osteomyelitis, found that when sequestrums were present it was necessary to remove them surgically to obtain satisfactory healing. These authors were able to secure an arrest of the disease with the disappearance of all local and constitutional signs of active infection in 70 per cent of their patients with chronic osteomyelitis. Prolonged therapy varying from two to six weeks was found to be necessary to achieve the best results. Occasionally the therapy had to be repeated when relapses occurred. The primary closure of wounds

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after sequestrectomy, together with the local administration of penicillin postoperatively, greatly shortened the recovery period.

Staphylococcal pneumonia has responded well to penicillin. In the absence of secondary foci recovery is usually complete in one to two weeks. The treatment of staphylococcal empyema with penicillin introduced into the empyema cavity has usually resulted in a decrease or disappearance of fever and a marked lessening of toxicity. In most cases, however, the exudate has not become sterile and thoracotomy has been necessary to effect full recovery.

### *Streptococcal Infections*

Hemolytic streptococcus infections are even more susceptible to the action of penicillin than are staphylococcal infections. In general the response has been similar to that seen with the sulfonamides, although in some cases the therapeutic effect has been even more rapid. Doses of 100,000 to 150,000 units a day are usually effective. Depending on the severity of the infection, treatment is continued until the temperature has been normal for two to five days.

Anaerobic streptococcus infections have been irregular in their response to penicillin since there is considerable variation in strain sensitivity to the drug. The sulfonamides are never effective in such infections, and a trial course of therapy with penicillin is indicated when such infections arise. Prolonged treatment may be necessary, particularly if there is an intravascular focus of infection, such as a thrombophlebitis.

Infections due to nonhemolytic streptococci that have been treated with penicillin have consisted almost wholly of cases of subacute bacterial endocarditis. Early attempts to treat this disease with penicillin were unsatisfactory because only small and inadequate doses could be given.<sup>65</sup> More recent experience, involving the use of doses of 200,000 to 300,000 units a day for periods of two or three weeks, has produced at least temporary arrest of the infection in more than 50 per cent of the cases.<sup>66-68</sup> From the evidence now available an initial course of treatment of 200,000 to 300,000 units a day for three weeks should be satisfactory in most cases. If by the end of a week the blood culture has not become negative, the dose should be increased. Patients who have relapsed after two or three weeks of therapy have been treated with more prolonged courses of treatment, with apparently successful results in a few cases. Cases have been encountered, however, in which it has been impossible to control the infection even when treatment has been continued for two or more months. The available evidence indicates that penicillin is just as effective in this disease when given by intermittent intramuscular injection as it is when given by continuous intravenous infusion. The use of heparin in con-

junction with penicillin has been recommended,<sup>66</sup> but this does not seem to be necessary and may constitute an added hazard to the patient.<sup>69</sup>

Strains of nonhemolytic streptococci vary in their sensitivity to penicillin, although the great majority are sensitive to the drug.<sup>35</sup> Enterococci, which cause about 10 per cent of cases of subacute bacterial endocarditis, are relatively insensitive to penicillin, and cases of endocarditis caused by these organisms have not responded to treatment. In view of the large amount of penicillin that must be given in bacterial endocarditis, it is advisable to investigate the sensitivity of the organism in each case before or at the beginning of treatment. In patients who relapse, the infecting organism usually has not shown a significant decrease in its sensitivity to penicillin.

It is of considerable interest that, for several weeks after the completion of treatment, patients whose blood cultures remain negative and who otherwise appear to be free of active disease have often exhibited petechiae and other embolic phenomena. In many of these patients the embolic phenomena have ceased after a short time and the patients have continued to remain well without further treatment. For this reason, it has been assumed that these episodes were caused by bland or sterile emboli. Occasionally embolism of a cerebral vessel has caused death. A few patients after recovering from the infection develop cardiac failure, which may progress and end fatally within a few months after treatment.

### *Gonococcal Infections*

The original observation by Mahoney et al.<sup>70</sup> that penicillin produces rapid and permanent cures in gonococcal infections has been fully confirmed.<sup>71</sup> About 96 per cent of gonococcal infections that are confined to the lower genital tract in either the male or female are cured by the administration of a total of 100,000 units of penicillin. The remaining 4 per cent usually respond to more intensive or prolonged treatment. No proved cases of penicillin-resistant gonorrhea have yet been encountered. Although varying schedules of administration have been used, the intramuscular injection of 20,000 units every two or three hours for five doses appears to be the most convenient. Such a treatment schedule is readily adaptable to office or outpatient practice. Gonococcal infections complicated by arthritis, prostatitis, salpingitis, epididymitis or endocarditis require more prolonged treatment. Whether penicillin is more effective than the sulfonamides in the treatment of gonococcal arthritis remains somewhat in doubt.

### *Meningococcal Infections*

Experience with the treatment of meningococcal meningitis has varied. Rosenberg and Arling<sup>72</sup> reported recovery in 65 of 66 patients treated with

penicillin. Their report, however, does not make clear how many of their patients received sulfonamides as well as penicillin. Meads et al.,<sup>73</sup> on the other hand, in a more critical study found that neither the bacteriologic nor the clinical signs of improvement were so rapid in patients treated with penicillin as in those treated with sulfonamides. Furthermore, 2 of their 9 patients treated with penicillin eventually required sulfonamide therapy to effect full recovery. At the moment, it appears that the sulfonamides are at least as efficient as penicillin in treating meningococcal meningitis and that they constitute a much more convenient and economical form of therapy. Penicillin may well be found useful in combination with the sulfonamides in the treatment of fulminating cases, and it is certain to have a place in the treatment of patients who do not respond to sulfonamide therapy or in whom sulfonamide treatment is contraindicated.

#### *Pneumococcal Infections*

Tillett<sup>74</sup> has shown that pneumococcal pneumonia and empyema respond readily to penicillin treatment. A dosage of 100,000 units a day for three or four days is adequate in most cases of pneumonia, although occasional patients require more prolonged and intensive treatment. Pneumococcal empyema has been treated successfully by injections of penicillin repeated daily or on alternate days for three to four injections. From the results now available, it seems that a high percentage of cases do not require surgical treatment. A thickened pleura with or without a sterile exudate may persist for several days or even weeks after treatment is completed. Organization of the exudate and permanent collapse of the lung may rarely develop, but the greatly shortened period of illness and disability that results from nonsurgical treatment is a strong endorsement for this form of therapy, provided the physician is alert for the possible appearance of the above-mentioned complications.

Pneumococcal meningitis has been successfully treated with a combination of intrathecal and intramuscular penicillin.<sup>74</sup> The fatality rate with such treatment in a large unselected series was approximately 55 per cent.<sup>75</sup> In a smaller group of cases, Waring and Smith<sup>76</sup> have reported the recovery of 11 of 12 patients following the combined use of penicillin and the sulfonamides. Although even combined therapy has failed in fulminating infections and cases that are treated late,<sup>29</sup> the use of both drugs appears to be rational and should give better results than when either drug is used alone. How long to continue therapy in this disease is a difficult question to answer, and undoubtedly the need for therapy varies from patient to patient. In cases that are treated with penicillin alone, it is usually necessary to continue intrathecal and systemic therapy for at least two weeks, but in occasional

cases it is necessary to continue treatment for many more weeks before the infection is eradicated.<sup>18</sup> When patients are receiving both penicillin and a sulfonamide, it has been possible to discontinue penicillin seven to ten days after beginning treatment, but it appears wise to continue the sulfonamide for at least two weeks after apparent recovery. The usual guides by which one measures progress may be lacking. After one or two days of intrathecal penicillin administration, the smears and cultures of the spinal fluid almost invariably fail to demonstrate the presence of organisms. It is known, however, that if treatment is stopped after the first negative bacteriologic reports are received, relapse is likely to occur. In certain patients who recover from the infection, residual damage to the central nervous system of greater or lesser extent has been observed.

Acute pneumococcal endocarditis can be successfully treated with penicillin, but the percentage of recoveries is not so great as in subacute bacterial endocarditis caused by nonhemolytic streptococci.

#### *Clostridial Infections*

The in-vitro activity of penicillin against the clostridial group of organisms has been confirmed by clinical studies. Jeffrey and Thomson,<sup>77</sup> in a study of 33 cases of gas gangrene treated with penicillin, found a mortality rate of 36 per cent. These authors emphasize, as do all other workers who have had experience with the problem, that the adequate surgical removal of all necrotic and devitalized tissue is the most essential therapeutic procedure in the management of gas gangrene. Five of their patients were seen late in the disease when surgery was not possible, and all of them died, despite treatment with penicillin. These authors believe that a dosage of 15,000 units every three hours for three to four days will control the infection in cases in which all the infected tissue can be removed surgically. In cases in which this is not possible, it is desirable to continue treatment for five to ten days. The administration of antitoxin is also of great value. Jeffrey and Thomson believe that with early and adequate surgery, aided by the administration of penicillin and antitoxin, the mortality rate in gas gangrene in battle casualties can be reduced to 20 per cent. Cutler and Sandusky<sup>78</sup> treated 7 patients with gas gangrene, 6 of whom recovered. It is noteworthy that in 5 of their patients gas gangrene developed while the patients were receiving prophylactic penicillin therapy. Following extirpation of the diseased tissues all these patients recovered.

A few cases of tetanus have been successfully treated with penicillin and antitoxin.<sup>79</sup> The group is too small to evaluate the role that penicillin played in recovery.

### Syphilis

In October, 1943, Mahoney et al.<sup>80</sup> reported on the favorable action of penicillin in the treatment of early syphilis. Following this report intensive studies of the treatment of early syphilis, neurosyphilis and congenital syphilis have been carried out by a group of co-operating clinics.<sup>81-84</sup> Final evaluation of their results will not be possible for several years. Preliminary reports indicate that a course of sixty injections of 20,000 units each given intramuscularly at three-hour intervals for seven and a half days probably represents the minimum dosage schedule that is effective in primary and secondary syphilis. It is not unlikely that more prolonged or more intensive treatment will prove to be necessary. Studies on neurosyphilis indicate that even larger doses are needed and that the results are much more irregular than those in early syphilis. Late cutaneous and osseous syphilis apparently respond promptly to penicillin treatment. No work has been reported yet on the action of penicillin in latent syphilis. A few cases of congenital syphilis have been treated in which good results have been obtained. It is agreed by all workers who are investigating the problem that the treatment of syphilis with penicillin is still in the stage of preliminary investigation and that no schedule of treatment can yet be recommended for routine therapy.

In the treatment of syphilis with penicillin, the incidence of Herxheimer reactions has been high. The reactions that have been observed have consisted of fever, malaise, headache, rash and painful swelling of the primary lesion and the regional lymph nodes. These reactions usually occur during the first day of treatment and disappear after twenty-four or forty-eight hours. They are not considered to be an indication for stopping treatment.

### Miscellaneous Infections

Most strains of *Actinomyces* are sensitive to penicillin, and a few cases of actinomycosis have been successfully treated.<sup>29</sup> Repeated courses are frequently necessary to keep the infection under control.

Anthrax responds well to penicillin, and it seems reasonable to predict that the drug will become the treatment of choice in this disease. Murphy et al.<sup>85</sup> have reported the successful use of penicillin in 3 cases of uncomplicated cutaneous anthrax. They believe that a dosage of 100,000 units a day for three or four days should be adequate in the average case. At least one patient with bacteremia has been treated, with a prompt and full recovery resulting.

The two causative agents of rat-bite fever, *Spirillum minus* and *Streptobacillus moniliformis*, are both sensitive to penicillin in the laboratory.<sup>86</sup> Clinical cases caused by the latter organisms have

been reported to respond favorably to treatment with penicillin.<sup>87</sup>

A preliminary report on the successful treatment of yaws with penicillin has recently been published.<sup>88</sup> One case of Weil's disease has been reported in which penicillin was administered and recovery ensued.<sup>89</sup> The author admits that the evidence that the drug had an effective therapeutic action in this case is not conclusive.

Penicillin is active in vitro against *Corynebacterium diphtheriae*. A few cases of clinical diphtheria have been treated with a combination of antitoxin and penicillin with results that are difficult to evaluate.<sup>90</sup> There is no reason to expect that penicillin will supplant antitoxin as the chief therapeutic agent in diphtheria. The supplementing of antitoxin with penicillin in cases of laryngeal diphtheria and diphtheria gravis may, however, prove to be valuable, although the evidence to support this procedure remains to be accumulated. Preliminary efforts to treat diphtheria carriers with penicillin have not met with success.<sup>91</sup>

Penicillin is already being adapted to the problems that are peculiar to various medical specialties. Dunnington and Von Sallmann<sup>92</sup> and Keyes<sup>93</sup> have reviewed the use of penicillin in ophthalmology. Infections of the conjunctiva and cornea usually respond well to local treatment when the infecting organism is susceptible to the action of penicillin. The drug may be administered in drops or in an ointment. Infections of the internal structure of the eye are more difficult to treat because of the poor penetration of penicillin. Special methods for administration, such as iontophoresis, the use of a corneal bath and direct injection of the drug into the anterior chamber of the eye, are usually necessary.

Swanson and Baker<sup>94</sup> have used penicillin in the management of acute otitis media, acute mastoiditis, acute labyrinthitis and chronic otitis media. When the infecting organisms are sensitive to penicillin, excellent results have usually been obtained. In selected cases penicillin therapy alone may be successful; in other cases surgical procedures must also be employed.

Johnson et al.<sup>95</sup> have shown that the local use of penicillin postoperatively in patients with acute mastoiditis permits the safe primary closure of incisions and greatly shortens the recovery period. Putney<sup>96</sup> has reviewed the successful use of penicillin in the treatment of some of the more serious complications of infections of the nose and throat. Sale and Diamond<sup>97</sup> have described the treatment of chronic suppurative maxillary sinusitis by local instillations of penicillin.

In the field of plastic surgery, Hirshfeld et al.<sup>98</sup> have reported that the systemic administration of penicillin greatly increases the percentage of successful skin grafts applied to infected surfaces.

The use of penicillin in infections of the skin

has been discussed by Roxburgh et al.<sup>99</sup> and by Taylor and Hughes.<sup>100</sup> Gingivitis and stomatitis caused by the Vincent's organisms have been effectively treated by the use of penicillin pastilles.<sup>101</sup>

#### PROPHYLACTIC ADMINISTRATION OF PENICILLIN

The prophylactic use of penicillin is just beginning to be studied. White et al.<sup>102</sup> have shown that penicillin administered intramuscularly for one week preoperatively and for two weeks postoperatively in doses of 150,000 units daily is of great value in preventing postoperative pyogenic infections following lobectomy or pneumonectomy. Their cases included patients on whom operation was performed for bronchiectasis, multiple lung abscesses, tuberculosis and carcinoma. In 21 patients treated prophylactically with penicillin, no cases of empyema developed, whereas in 20 control patients, 12, or 60 per cent, developed pleural suppuration. Cutler et al.,<sup>103</sup> on the other hand, in a study of the prophylactic use of penicillin in conjunction with early definitive surgery in wounds sustained in aerial warfare did not find that the use of penicillin lowered the incidence of infected wounds.

#### DISEASES UNINFLUENCED BY PENICILLIN

A review of the present status of penicillin therapy would not be complete unless it included mention of those diseases in which penicillin has not proved to be of therapeutic value. The list of such diseases, as compiled by Keefer,<sup>104</sup> is reproduced, with additions, in Table 3.

Since penicillin has no effect against infections caused by gram-negative bacilli, it is not to be ex-

TABLE 3. *Diseases in Which Penicillin Therapy is Ineffective.*

All gram-negative bacillary infections	Coccidiomycosis
Tuberculosis	Malaria
Toxoplasmosis	Poliomyelitis
Histoplasmosis	Blastomycosis
Acute rheumatic fever	Nonspecific iritis and uveitis
Lupus erythematosus (diffuse)	Moniliasis
Infectious mononucleosis	Virus infections
Pemphigus	Cancer
Hodgkin's disease	Rheumatoid arthritis <sup>105</sup>
Ulcerative colitis	Granuloma inguinale <sup>106</sup>
	Leukemia (acute and chronic)

pected that the drug will prove to be of value in the treatment of peritonitis following a ruptured viscus, except in those cases in which organisms sensitive to penicillin happen to play a significant role. Fauley et al.<sup>107</sup> have reported that penicillin given early will completely control experimental peritonitis in the dog. These workers, however, do not include any bacteriologic findings in their report.

#### TOXIC REACTIONS

Despite the greatly increased clinical experience with penicillin during the past year, no reports have appeared to cause any revision of the early

opinion regarding the drug's lack of significant toxicity for man. To date no harmful effects on the liver, kidneys or hematopoietic system have been observed following its administration. A few minor untoward reactions have been encountered.

From 2 to 5 per cent of patients treated with penicillin develop urticaria. The urticaria may appear on the first day of treatment, or it may not become apparent until several days after treatment has been completed. It usually develops during the second week of treatment. Occasionally it may be quite severe, but in most cases it is mild and frequently disappears even though treatment is continued. If penicillin is administered at a later date to a patient who developed urticaria with a previous course of treatment, urticaria may or may not reappear. Most workers do not believe that urticaria is a contraindication to the continuation of treatment or to the readministration of the drug at a later date. In the rare case in which urticaria is marked, the patient's severe discomfort may necessitate stopping treatment.

Much more unusual is the appearance of an erythematous vesicular rash.<sup>108</sup> I have seen a patient in whom a very severe rash of this type appeared twenty-four hours after the beginning of treatment in areas where there had been a severe ringworm infection four years previously.

Pain on intramuscular injection is encountered with varying frequency. It has been shown conclusively that impure preparations are the most irritating.<sup>16</sup> There is also no question that the technic of administering the drug has much to do with the amount of discomfort or lack of discomfort that occurs. When a portion of the drug is given subcutaneously by error, the degree of discomfort appears to be increased.

I have seen 4 cases in which foot drop developed in patients who were receiving intramuscular injections of penicillin into the buttocks. For this reason, great care should be taken to avoid injecting penicillin into the sciatic nerve or its immediate neighborhood. If the upper outer quadrants of the buttocks are used for the injections, the nerve should be easily avoided.

After multiple intravenous injections, thrombosis of the veins at the sites of the injection may occur. This event appears to be related more to the technic of performing the venipunctures than to irritation from the injected solution. In patients receiving the drug by a continuous intravenous infusion, however, the development of a painful thrombophlebitis in the vein being used is not infrequent. This reaction is often accompanied by chills and high fever. Changing the needle to another vein usually does not relieve the symptoms, and in most cases it becomes necessary to change from the intravenous to the intramuscular route of administration.

The penicillin preparations that are now being distributed are tested for pyrogens before being

released by the manufacturers. The febrile reactions due to impurities in the drug that were occasionally encountered in the early days of penicillin treatment are no longer seen. Drug fever analogous to that seen in sulfonamide therapy has not been reported. Occasionally patients have been observed who maintain a low-grade fever after the clinical signs of infection have disappeared. In several of these cases, the temperature has returned to normal when penicillin was discontinued.

In rare cases the administration of penicillin has been accompanied by diarrhea, with or without abdominal cramps. Nausea and vomiting caused by penicillin have not been described. On the contrary, a return of appetite is one of the earliest signs of a favorable response to penicillin therapy. With the use of some of the early preparations various minor reactions were seen from time to time, including headache, flushing of the face and pain in the testes. With the preparations now in use, these reactions are not being reported.

The maximum dose of penicillin that can be given safely to man has not yet been determined. Doses as large as 4,000,000 units a day have been given in several cases without ill effect. At present there are no known contraindications to the administration of penicillin, although there may be reason for hesitation in administering large initial doses to patients with cardiovascular or congenital syphilis. So far as is known, penicillin is not incompatible with any other drugs or articles of diet.

\* \* \*

Penicillin has been shown to be a potent, nontoxic, antibacterial agent against many important pathogenic bacteria. In the treatment of almost all infections caused by these organisms, penicillin is the most effective chemotherapeutic agent that has yet been discovered. Its use in many of these infections, either alone or in combination with other established forms of therapy, has resulted in a lowering of the mortality rates, a shortening of the periods of illness and a reduction in the number of complications. In many diseases, sufficient experience has accumulated to permit the formulation of fairly definite concepts regarding the effectiveness of penicillin and the best methods for its employment. In other infections, experience has been limited to a few experimental efforts that merely hint at the possibilities of penicillin therapy.

In the treatment of infections with penicillin, early treatment, adequate dosage and the continuation of treatment until the infection is eradicated are essential for obtaining the maximum results. Likewise, in planning therapy, proper consideration must be given to the known facts concerning the absorption, excretion and distribution of penicillin in man. In many cases the concomitant use of other therapeutic procedures of established value, including general supportive measures, sur-

gery and the administration of specific antisera, are necessary to effect recovery.

The drug cannot be expected to have a favorable effect on the course of diseases other than those infections in which the causative organisms are known to be susceptible to the action of penicillin.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31151

#### PRESENTATION OF CASE

A twenty-four-year-old farmer entered the hospital because of severe sacral pain.

Two months before entry, without known preceding trauma, he began to have intermittent dull, aching pain in the right half of the sacrum. Two weeks later he received three blows over this area that caused severe pain. Following this the pain persisted, was sharp and was aggravated by motion, coughing and sneezing. X-ray studies of the lumbosacral spine six weeks before entry were allegedly negative.

One month before admission he spent ten days in a community hospital, where he was found to have fever and slight leukocytosis; he had no bowel movements for eight days. During the month before entry his back had been stiff and cutting pains began to occur, extending across the shoulders and in the arms. These lasted from a few minutes to several hours. One week before admission he felt "pins and needles" in his right hand, arm and shoulder, and a sharp pain just below the right costal margin. The pain frequently shot from the lower back down the posterior aspect of the right leg to the heel. He had spent most of the month preceding entry in bed and finally could scarcely move because of pain. During the earlier part of his illness he lost 25 pounds. He had become extremely weak. For about a month he had noted some difficulty in starting the urinary stream.

Physical examination revealed an emaciated, anemic-looking man who complained of excruciating pain in the lower back on the slightest motion.

\*On leave of absence.

There was generalized muscle wasting, most pronounced in the thighs. There were splinting of the chest and marked spasm of the abdominal muscles, with slight, diffuse abdominal tenderness and marked tenderness of the lower thoracic and lumbar spine and over the right sacroiliac joint. The knee and ankle jerks were diminished on the right side. The arm jerks, abdominal reflexes and plantar reflexes were normal. Sensation was normal. There was slight generalized lymphadenopathy. The heart and lungs were not remarkable.

The temperature was 99°F., and the pulse and respirations were normal. The blood pressure was 128 systolic, 68 diastolic.

Examination of the blood showed a red-cell count of 4,250,000, with 12.2 gm. of hemoglobin, and a white-cell count of 12,000, with 88 per cent neutrophils. The differential count and cell morphology were normal. The urine was normal, containing no Bence-Jones protein. The stools were guaiac negative. The serum calcium was 8.5 mg. per 100 cc., the phosphorus 4 mg., and the phosphatase 4.7 Gutman<sup>1</sup> units per 100 cc. The serum protein was 6.3 gm. per 100 cc. The sedimentation rate was 53 mm. in one hour. Hinton and Wassermann reactions were negative. A lumbar puncture revealed an initial pressure equivalent to 250 mm. of water and normal dynamics; the fluid was clear and colorless and contained no cells, the total protein being 21 mg. per 100 cc.

X-ray examinations revealed slight irregularity of the margins of the dorsal vertebrae and of the sacroiliac joints, which were thought to be consistent with rheumatoid arthritis. There was some increased density of the cortices of the internal condyles of the tibiae. A chest film, gastrointestinal series and barium enema were negative. X-ray films of the knees and shoulders were normal.

The pain in the lower back and sacral region continued to be severe. There was occasional urinary and fecal incontinence. The temperature was slightly elevated most of the time, but it was rarely over 100°F., although it did reach 102° on one occasion. The pulse averaged 90, and the respirations remained fairly constant at 20. One week after admission he was awakened by a severe steady pain in the right flank, radiating to the groin and testicle but not to the penis. This lasted twenty minutes. He admitted that he had previously had similar



attacks, always on the right side. The right knee jerk became progressively less active. Two weeks after admission a firm, tender swelling measuring 6 cm. in diameter and elevated 1 to 2 cm. was noted on the upper part of the sacrum to the right of the midline. Additional films of the sacrum and lumbosacral junction showed an area of apparent destruction in the posterior superior spine of the ilium, where it articulated with the sacrum.

On the eleventh hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. WILLIAM A. ROGERS: May we see the x-ray films?

DR. MILFORD D. SCHULZ: The irregularity described in the dorsal spine looks more like old epiphysitis than anything else. The films show the lumbar spine and the dorsal spine to be otherwise normal, but on the film of the pelvis there is shown an area of rarefaction in the right wing of the sacrum that is indefinite in outline. It does not have sharp borders, and whether it is primary in the sacrum or the result of destruction by something metastatic to it cannot be determined on the information we have.

DR. ROGERS: I agree that the roentgenogram of the thoracic vertebrae in the lateral view reveals an old epiphysitis and is not suggestive of other diseases that might involve the thoracic region, such as, tuberculosis and the rheumatoid group of vertebral-column conditions. The changes are not consistent with trauma, nor is there evidence of pyogenic infection. In the anteroposterior view of the lumbosacral region there is a suspicious area of increased radiability in the right ilium, near the sacroiliac joint, without definite demarcation. There are no appreciable margins about this area. The films are far from conclusive, however, by reason of the circumstance that the gas patterns overlying the right side of the sacrum are such as to make it quite difficult to be certain of definite bone change. The lateral view of the lumbosacral junction does not look abnormal.

The salient features in this case seem to be the patient's age, twenty-four years, and his incapacity of months rather than of days. There was a temperature elevation that averaged 100°F. but had not been over 102, and concomitant with this, the white-cell count had not exceeded 12,000 or, what is more important, it did not go over 15,000. I am struck with the circumstance that he had not only excruciating local pain but also corresponding referred pain, that is, to the posterior aspect of the thigh and leg. Consistent with the referred pain was the sharp diminution in the ankle jerk. The diminished knee jerk is not attributable to a lesion of the first sacral segment, as is the diminished ankle jerk, since it corresponds to the third lumbar segment.

It may have been due to the wasting that was apparent in the quadriceps muscle. We also know that this patient had a good deal of urinary and rectal incontinence. There again, these functional changes are consistent with a serious deep lesion in the sacrum. We also know from the history that this man developed severe pain in the right flank that was accompanied by pain in the ilioinguinal and iliohypogastric distribution, the right groin and the testicle. This distribution of referred pain is consistent with a lesion of the right flank that may be in the right upper lumbar gutter, or it may come from the vertebral column — the twelfth thoracic or first lumbar segment. But the appearance of the twelfth thoracic and first lumbar vertebrae in the roentgenograms does not suggest the presence of a lesion. The films are not too good, but it should be remembered that the man was in excruciating pain, associated with extensive splinting of the thorax and the abdomen, which might make it difficult to place him in the correct position for good films.

Another salient feature in this case is the splinting in the chest and abdomen. It is an outstanding clinical sign. The splinting is a reflex mechanism protecting either the contained viscera or the vertebral column or meninges in the thoracic or lumbar region. When extreme, it is suggestive of meningeal irritation. Lastly, he had no definitely localizing symptoms other than the subjective one of pain in the right side of the sacrum until several days before operation, at which time he developed a firm sizable mass in the upper half of the sacrum on the right side.

Are we dealing with infection, with congenital malformation, with injury, with new growth or with some metabolic disturbance, such as rheumatoid arthritis?

From the standpoint of acute infection, a pyogenic infection could have been the primary cause of this man's trouble. All pyogenic infections are not fulminating, and all do not produce a high elevation of the temperature or white-cell count. Against acute pyogenic infection, however, is the duration, two months, without evidence of abscess formation. Certainly roentgenograms taken one month following acute pyogenic infection of the sacrum should show changes. Usually a history of two or three days is consistent with osteomyelitis. The possibility of osteomyelitis of the sacrum is, however, real, but I do not believe that it is likely. In the chronic infections we have to consider syphilitic osteitis. We know that the Hinton and Wassermann reactions were negative. Tuberculosis should certainly have responded favorably to rest in bed for a month; instead the patient grew steadily worse, his symptoms intensified, and finally the mass appeared. Although this could have been a cold abscess, I believe that the likelihood of tuberculosis is not great.

Among the congenital malformations, low leptomeningeal and cauda-equina lesions can be ruled out by the absence of symptoms prior to two months ago and by the lumbar-puncture findings.

I am far more impressed by the probability of neoplasm in this case. Among the primary tumors, Ewing's tumor would be consistent with the temperature elevation and the leukocytosis. On the other hand, the patient was twenty-four years old, and Ewing's tumor usually, but not always, occurs in the first two decades. Furthermore, Ewing's tumor is usually confined to the shafts of the long bones, although it may occur in the pelvis and may be purely osteolytic. I am inclined to think that this is not a Ewing's tumor, although it is a possibility.

Multiple myeloma must also be considered. The lesion of multiple myeloma is rather apt to be circumscribed, and although it may be solitary for many months or even several years, it would scarcely give the roentgenographic appearance that this case shows.

Neuroblastoma produces osteolytic bone lesions. It is a possibility in this case but does not explain the fever or leukocytosis.

Of course, osteolytic bone sarcoma must be considered. The patient was on the borderline between the young and the old group, so that he could have had an osteolytic sarcoma from any of the elements of the bone. A tumor of the lymphosarcoma group, which includes lymphocytoma, lymphoblastoma and reticulum-cell sarcoma, would not be inconsistent with the findings in this case. There is not uncommonly fever with lymphosarcoma, and such a tumor might cause severe local pain in the right flank.

Because of the pain in the groin and testicle, renal-cell carcinoma should be discussed. This produces an osteolytic lesion in the bone and frequently metastasizes to the pelvic bones. There might have been a rupture of some of the rapidly growing cells in the renal region through the cortex of the cancer, with the initiation of the intense local and referred pain. This tumor, however, is not usually associated with fever. Many other carcinomas may metastasize to the pelvic bones.

In summary, I am inclined to favor neoplasm — either a lymphosarcoma as a primary lesion or a metastasizing osteolytic tumor, such as a renal-cell carcinoma, as a secondary lesion. It is possible that this man had a pyogenic infection or tuberculosis of the sacrum; he might even have had rheumatoid arthritis, but I believe that Dr. Ropes would agree that it is a rather atypical picture of rheumatoid arthritis.

DR. RONALD C. SNIFFEN: Dr. Kubik, will you outline the terminal course regarding the neurologic findings?

DR. CHARLES S. KUBIK: As stated in the abstract, the patient had had pain between the shoulder blades and some numbness in the fingers. Several days after the biopsy, in the course of about two

hours, he developed complete motor and sensory paralysis below the fifth thoracic level; following that he never again had pain below that level but continued to have extremely severe pain in the upper thoracic and lower cervical spine, in the upper part of the chest and in the arms. There were times when he had to be given 65 mg. of morphine subcutaneously every hour. He developed marked weakness and atrophy of the arms and hands and tumor masses in the occipital region. He died about two and a half months after entry or about two months after the biopsy.

DR. WYMAN RICHARDSON: I looked at a blood smear before I saw this patient and was therefore unprejudiced. The smear showed a picture consistent with acute blood loss or tumor involving the bone marrow. Unfortunately I did not describe the smear in the record, but it showed a slight leukocytosis, with an increase in immature red cells and no toxic changes in the neutrophils, which suggested that no infection was present. There was something causing an increased output of cells from the bone marrow. Hemorrhage could have done that, but there was no history of hemorrhage. Therefore, by exclusion, some form of marrow tumor seemed likely. This diagnosis seemed to fit best with the clinical picture. I thought that the likeliest tumor was some type of lymphoma.

#### CLINICAL DIAGNOSIS

Malignant tumor of ilium.

#### DR. ROGERS'S DIAGNOSIS

Malignant neoplasm, ? lymphosarcoma.

#### ANATOMICAL DIAGNOSIS

Ewing's tumor of sacrum, with widespread metastases.

#### PATHOLOGICAL DISCUSSION

DR. SNIFFEN: We made a diagnosis of "probable synovium" on the biopsy material. After reviewing the section I was rather surprised that we gave it a name, for the section was poor and the tumor was undifferentiated.

The patient died eighty-three days after admission. He was extremely emaciated and had a severe anasarca, which included peripheral edema, ascites, hydrothorax and hydropericardium. The muscles of the right arm were atrophic. Over the sacrum on the right there were two decubitus ulcers. The right wing of the sacrum was destroyed by a tumor measuring 6.5 cm. in diameter. The right occipital bone contained a tumor of the same size, and the cerebral dura was studded with nodules that had penetrated that membrane but not the underlying arachnoid. At one point the superior longitudinal sinus had been invaded by the neoplasm. Otherwise the brain was unchanged, except for signs of in-

creased intracranial pressure. The spinal column from the fourth to eighth thoracic vertebra contained tumor, which had penetrated the epidural space and dura but not the arachnoid. The same situation prevailed for a distance of 13 cm. below the twelfth thoracic vertebra. Microscopic sections of the spinal cord showed early ascending and descending degeneration from about the midthoracic level. The ribs contained multiple tumor nodules. The lungs, liver, kidneys, pancreas and retroperitoneal and mesenteric lymph nodes were studded with metastatic nodules averaging a centimeter in diameter, with a maximum size of 4 cm. The adrenal glands weighed 26 gm. together, and each contained several small masses of tumor.

Microscopically the tumor was composed of undifferentiated cells with large, vesicular nuclei and an occasional nucleolus. The cytoplasm was scant and poorly defined. The cells were divided into groups by strands of delicate fibrous tissue. Our diagnosis was Ewing's tumor.

It is interesting to speculate on the origin of this type of tumor. Does it arise from the vascular endothelium, as Ewing<sup>2</sup> believed? Does it belong in the reticulum-cell-sarcoma group? Is it a bone tumor? One of the more recent ideas is that many of the neoplasms labeled Ewing's tumor are, in reality, metastatic neuroblastoma, a tumor originating from the primitive cells of the sympathetic nervous system. This theory was proposed by Colville and Willis<sup>3</sup> in 1933 and again by Willis<sup>4</sup> in 1940, who point out that there is no satisfactory clinical or roentgenographic distinction between Ewing's tumor and neuroblastoma and that radio-sensitivity is not of real value in differentiating the two. Their first case was quite similar to the one under discussion except that the main and presenting tumor was in the thigh; the adrenal glands contained tumor nodules. The second patient had two large tumors, one in the thigh and the other in the line of the lumbar sympathetic chain, which ran through it. They cite the well-known papers of Hutchison<sup>5</sup> and Pepper,<sup>6</sup> who wrote of patients having small adrenal neuroblastomas with massive metastases to the skull or liver, which might have been mistaken for the sites of the primary tumor. It is unusual for a primary bone tumor to metastasize to lymph nodes as Ewing's tumor does so frequently. The complete confusion in the literature regarding the origin of Ewing's tumor cannot be denied.

Regarding the histology of these tumors, in neuroblastoma one often finds an arrangement of cells and fibrils that has the same configuration as the cells from which the sympathetic nervous system and the adrenal medulla develop. One mode of arrangement is in the form of a rosette—a ball-like aggregate of cells enclosing a meshwork of fibrils. These were beautifully demonstrated by Wright<sup>7</sup> in 1910, and Colville and Willis found

rosettes in their cases. In neuroblastoma one may find more highly differentiated tissue in the form of ganglion cells, but Colville and Willis were unable to demonstrate such areas in their cases.

If there is truth in this theory, several practical points come to mind. Should amputation be undertaken if one is dealing with a metastatic tumor? Should routine roentgen therapy be given to the retroperitoneal tissue when a diagnosis of Ewing's tumor has been made after biopsy of a bone? Certainly the retropleural and retroperitoneal tissues should be investigated thoroughly in view of the fact that they may be harboring the primary tumor.

To come back to this case, and to reach no conclusion, I could find no resemblance between this tumor and a neuroblastoma. Therefore the diagnosis must rest at Ewing's tumor.

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#### CASE 31152

##### PRESENTATION OF CASE

A thirty-six-year-old graduate nurse was admitted to the hospital because of irregular and profuse menstrual bleeding.

From the time of the menarche, at the age of sixteen, the menstrual periods were irregular and profuse, with considerable loss of blood on each occasion. At times there were long free intervals. At the age of twenty an appendectomy was performed, and a tube, said to be tuberculous, was removed. Following this she had long stretches of amenorrhea, followed by profuse bleeding, occasionally with clots, requiring eight to ten napkins a day for seven days. She received a variety of endocrine preparations, with no apparent effect until about four years prior to admission, when, following the administration of Antophysin, her periods became regular and normal for about two and a half years but then again became infrequent and profuse. For six months preceding entry she had had almost continuous flow.

The patient had always been obese, averaging 230 pounds. Two years before entry, while on a diet, she lost 75 pounds, but she had subsequently regained 50.

The patient's father died of tuberculosis when she was three years old, and a younger sister had pulmonary tuberculosis.

Physical examination revealed an obese woman in no acute discomfort. The skin was warm. There was no palpable adenopathy. The fundi were normal. The thyroid gland was not enlarged. The breasts were pendulous. The heart and lungs were negative. Slight tenderness was present on deep palpation in the left lower quadrant of the abdomen. A pelvic examination revealed a slightly enlarged uterus but was otherwise not remarkable.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 74 diastolic.

Examination of the blood revealed a red-cell count of 3,570,000, with 10 gm. of hemoglobin, and a white-cell count of 5100, with 66 per cent neutrophils, 27 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils. There were no significant red-cell abnormalities on smear. The urine had a specific gravity of 1.020 to 1.030, with a 0 to + test for albumin; a few white cells were found in the sediment. The serum nonprotein nitrogen was normal, and the protein 5.9 gm. per 100 cc. A glucose tolerance test revealed a fasting level of 105 mg. per 100 cc., which rose to 185 mg. at the end of two hours and to 162 mg. at the end of three hours. The basal metabolic rate was +1 per cent. A blood Hinton test was negative. A tuberculin test (dilution unknown) was strongly positive.

Roentgenographic examinations of the skull, spine and urinary tract were negative.

On the fifth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. FRED A. SIMMONS: Since this is a teaching clinic, I am going to mention a few points that might be instructive regardless of what the diagnosis may be. In any patient who is bleeding, no matter what age, we should include the tests that are available today for the ruling out of malignant disease. The most frequently practiced and probably the most accurate test at the moment is a diagnostic dilatation and curettage including cervical biopsy. We also have a fairly accurate test, the vaginal smear, which should have been carried out on this patient.<sup>1</sup> The laboratory has now studied vaginal smears from over 1200 cases, with an error of only 4 per cent in 95 cases of proved cancer. The point I am making is that anyone with this history should have cancer ruled out. I assume that this was probably the operation that they intended to do. I should also like to point out that in handling patients with profuse flowing at thirty-six years of age, a dilatation and curettage might better be carried out before giving any endocrine preparation. The assumption that Antophysin regulated the menstrual cycle implies that it was on an endocrine basis, but malignancy still cannot

be ruled out. Antophysin is a proprietary name for chorionic gonadotropin.

That the patient had tuberculosis is quite likely in view of the family history and because of the reported tuberculous tube removed at the age of twenty. I believe that the general opinion of gynecologists in most parts of the country is that the proper treatment for such a condition, if it really were a tuberculous tube, is radical surgery, which would include removal of the uterus and both tubes and ovaries, since the process is apparently a hematogenous infection. This patient, according to the record, had no other signs of tuberculosis, and I rather doubt that she had it. I question then the pathological report of the operation at twenty years of age. Another thing that bothered me was that from the physical findings presented here I was unable to determine whether the patient had been married and whether she had ever borne children. It is fair to point out that the pelvic examination should include some comment whether the patient had a virginal or multiparous introitus.

DR. BENJAMIN CASTLEMAN: The record merely states that the patient was unmarried.

DR. SIMMONS: This fact does not help me unless it is fair to assume that she was a virgin, in which case I shall not go into the possibility of inflammatory disease other than tuberculosis. Of course, irregular bleeding of this nature can be due to gonorrhea and its sequelae. A pelvic examination should also include inspection of the cervix. All that may have been left out for the sake of brevity.

In summary, I am inclined to consider the tuberculous history and findings in the tubes to be irrelevant, although I cannot rule out tuberculous endometritis as the cause of the trouble. I am inclined to think that she did not have carcinoma, because she had lived so long with a history of bleeding. If we can believe the menstrual-cycle history, the amenorrhea followed by profuse flow is the perfect picture of functional uterine bleeding, metropathia hemorrhagica, endometrial hyperplasia or whatever you want to call it.

Metropathia hemorrhagica is a term applied to a specific type of functional uterine bleeding characterized by a state of continuous estrinism with hypoprogestinism, according to Albright.<sup>2</sup> It is frequently seen in women with general debility regardless of age, presenting itself as alternating amenorrhea followed by continuous flowing, usually without molimen and dysmenorrhea, which may have been present in the patient's normal menstrual cycle. Pathologically the endometrium is markedly thickened, with deep glands having the "Swiss cheese" appearance characteristic of the estrin effect.

Endometrial hyperplasia or what I prefer to call "endometrial dysplasia" is the pathological term applied to the clinical state described above. Func-

tional uterine bleeding or dysfunction of uterine bleeding refers to the abnormal state of flow, with or without amenorrhea, not precipitated by organic pathological disease and is a convenient pigeonhole for cataloguing vague irregular states of uterine bleeding.

I think that on the whole it is wise to suggest the need for diagnostic dilatation and curettage and biopsy. I shall make a diagnosis of endometrial hyperplasia on an endocrine basis; possibly there was a benign endometrial polyp.

DR. FRANCIS M. INGERSOLL: I agree entirely with the diagnosis of metropathia hemorrhagica associated with a hyperplastic endometrium; however, we often see patients with the same history in whom the endometrium is atrophic rather than hyperplastic. Apparently about 20 to 30 per cent of them originally had an overfunctioning endometrium.

#### CLINICAL DIAGNOSIS

Metropathia hemorrhagica.

#### DR. SIMMONS'S DIAGNOSIS

Endometrial hyperplasia (metropathia hemorrhagica?).

#### ANATOMICAL DIAGNOSIS

Tuberculous salpingitis and endometritis.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The operation was a curettage, and a large amount of endometrium was removed. The diagnosis on microscopic examination proved to be tuberculosis. Following that operation a laparotomy was performed and the other tube and uterus were removed. We found tuberculosis in both the uterus and tube.

DR. INGERSOLL: Did they take out the cervix? I remember one case in this hospital in which someone first removed one tube, than at a subsequent operation took out the other tube and did a supravaginal hysterectomy and finally did a cervicectomy for tuberculosis.

DR. CASTLEMAN: The cervix was removed in this case.

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## GOVERNMENTAL SUPPORT FOR MEDICAL RESEARCH

SENATOR PEPPER, as chairman of a subcommittee of the Senate Committee on Wartime Health and Education, recently held a hearing at which a number of highly qualified persons were invited to discuss the question whether the federal government should continue in time of peace, as in war, to offer assistance through grants or in other ways to facilitate progress against disease through research. The Senator did not consider it possible or desirable for the Government to do all the work that its funds would finance. He was interested in determining how the universities, industries and the Government

could best co-operate to achieve the highest development of medical research. Some of the information and opinions brought out at this hearing are of considerable interest.

Brigadier General J. S. Simmons, chief of the Preventive Medicine Service, Office of the Surgeon General, was the first person to be called. He said that one of the most important factors contributing to the excellent record of the Medical Department of the Army during this war has been the unique emphasis placed by the Surgeon General on the necessity for research in all fields of medicine. The comprehensive research program that has been developed and carried out by both military and civilian scientists has produced a wealth of new and fundamental knowledge and resulted in improved methods for the care of the wounded and the prevention and treatment of many of the diseases that afflict troops. The program included investigations in three general categories: projects developed within Army laboratories and field installations; projects developed in civilian institutions under Army contracts negotiated through the Office of the Surgeon General and projects developed for the Army in civilian institutions under contract with the Office of Scientific Research and Development. On the whole, the civilian response and the results obtained during the war afford an inspiring example of what can be accomplished through a well-organized, co-operative research program.

He said that the new knowledge made available had been immediately applied in the field. Three groups of studies were mentioned, any one of which more than justified the total cost of the program — those concerning the development of blood substitutes, of penicillin and of insect repellents and insecticides. In addition, new methods of immunization and other means of prophylaxis have considerably reduced the incidence and mortality of most of the important infectious diseases. The new weapons developed for the fight against these diseases, moreover, have also revolutionized the foreign quarantine program of the Army, Navy and Public Health Service, and they afford better methods for the protection of this country, particularly against insect-borne diseases and their vectors.

General Simmons suggested that plans for postwar medical research as it affects the Army should be based on the following assumptions: that the security of the Nation depends on the health and physical strength of its people, both military and civilian, and that a continuing program of research on military medicine is essential to this security; that the Army will undertake research of importance to the Army in peace or in war and will share the responsibility but, of course, will not attempt to assume the full burden in those fields common to the military and civilian components of the Nation; that in studying medical problems of significance to the Army full use will be made both of the research facilities within the Army and those made available in certain civilian institutions, the Army directing its attention chiefly to problems which can best be carried out under military conditions; and that the need for medical research by and for the Army bears no direct relation to the size of the Army, since the medical problems of future wars must be anticipated.

Brigadier General Stanhope Bayne-Jones, deputy chief of Preventive Medicine Service, Office of the Surgeon General, described the organization and work of the Board for Investigation and Control of Influenza and Other Epidemic Diseases. It consists of a central board, composed of seven members, and ten commissions, which include about a hundred civilian consultants to the Secretary of War, all of whom are experts in their special fields. These consultants are on a part-time basis and are stationed at their home institutions, but they are called to duty under orders issued through the Office of the Surgeon General. They have worked on more than a hundred projects in Army camps and posts, both in this country and overseas. The plans for postwar medical research now under consideration in the Office of the Surgeon General contemplate not only a continuation of research by the Medical Department itself but also the organization, co-ordination and support of medical research on a national scale.

Dr. A. N. Richards, chairman of the Committee on Medical Research of the Office of Scientific Research and Development, described the work of that committee and brought out the need for some such

governmental organization. His committee has discharged its duties through contracts made by the Office of Scientific Research and Development on a "no loss, no gain" basis with colleges, universities, hospitals, research institutions and research groups in commercial companies, as well as through transfer of funds to other agencies of the Government. The contracts cover reimbursements not only for items of equipment, supplies and salaries of assistants but also for salaries of the chief investigators. Nearly five hundred contracts with one hundred and twenty different institutions have been made by this committee, and these involved almost twenty-seven hundred persons, of whom about one fifth were physicians. For the three years ending June 30, 1944, the expenditures for these contracts in successive years amounted to \$2,342,440, \$5,260,110 and \$7,747,276. None of the universities engaged in this work could have undertaken the projects at the expense of their own resources on the scale that the emergency demanded.

The difficulties that Dr. Richards anticipates in developing a peacetime program of this kind are as follows: the vastly broader and more perplexing choice of problems to be studied; the need for a stimulus to replace the ardor for service that imminent national danger has provided, and the need for a type of governmental control so understanding and so flexible that the imagination and scientific passion of investigators will not be dampened; and the increasing difficulties in choosing the institutions to which support shall be given and the definition of the terms with which it shall be offered. He suggested that a thorough survey be undertaken, not only of medical schools and associated hospitals but of the science departments of their universities.

Dr. Lewis H. Weed, chairman of the Division of Medical Sciences, National Research Council, reviewed the work being supported by that council and also described the difficulties that the institutions receiving this aid had experienced in obtaining financial support before the war. He prophesied that in the postwar period it would be even more difficult to obtain the necessary funds. He was convinced that much of medical research will necessarily have to be abandoned in the private and semiprivate institutions of the country unless

governmental subsidies are made available in some form for their support. He thought, however, that any administrative organization created by the Government should take cognizance of the total problem rather than serve merely as a mechanism for handling funds for medical research. It should be an independent agency with broad advisory functions. He added that medical research cannot, in the long run, be divorced from medical schools, from hospitals, from medical practice and from preventive procedures and matters of public health.

Dr. David Heyman, president of the Board of Directors, New York City Public Health Research Institute, described his organization, which he hoped would set a pattern that might be widely followed. This institute is closely associated with the New York City Department of Health but is a completely independent institution. It is governed by its Scientific Council, which initiates and supervises scientific projects, and its Board of Directors, which sets general policies and controls finances. It is financially assisted by the city under a long-term contract but also receives funds from private donors.

Dr. Heyman pointed out the limitations of the various foundations, whose support is necessarily restricted because of their limited resources and because their benefits are spread over a wide field. These foundations usually hope that, when something begins to turn out well, further support will be given by the public and by a governmental agency. He stated that the Government should support medical research by making grants-in-aid to existing nonprofit institutions rather than by setting up new laboratories of its own. In this way, it can provide opportunities for continued service by the many able young scientists now in the armed forces and also provide training for youths who show promise.

From the testimony of these experienced persons, it is obvious that some sort of wide support for medical research must be provided by the federal government if advances in this field are to continue. Incomes from private endowments have dropped off markedly, and the prospects of new funds from similar sources are not particularly good and certainly cannot be expected to keep pace with the

growing needs of medical research. During the past decade manufacturers of pharmaceutical and other products have filled some of the gap by generous support of projects in which they have special interests. They have also developed research organizations of their own that are rapidly becoming pre-eminent in the field of medical research. They cannot, however, be expected to carry too much of the burden, which in the long run rightly belongs to all the people, who are the beneficiaries of the results of this research.

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### THE DOCTOR ILLUSTRATES HIS TRAVEL NOTES

Young Richard Bright, son of a well-to-do Bristol banker and a student in medicine at Edinburgh, went on an expedition to Iceland at the age of twenty-one. With his gifted pen he not only described the botanical and zoological specimens collected by the Mackenzie party, but he also drew some of the illustrations contained in *Mackenzie's Travels in Iceland*, published in 1811. After graduating from Guy's Hospital in 1812, moreover, Bright toured Holland, Belgium and Germany and spent the winter of 1814-1815 in Vienna. His *Travels from Vienna through Lower Hungary*, published in 1818, contains an account of his wanderings and, again, as in the Iceland tour, he drew his own illustrations. Bright's book is perhaps the most worthy of all self-illustrated travel books by a doctor, but many other physicians, both before and after his time, enlivened their accounts with sketches or paintings. Three other examples may be given, two of which are the product of men whose names are household words in medicine.

William Macmichael, also a son of a banker, became a Radcliffe Traveling Fellow from Oxford in 1811. He made several journeys to Russia and Turkey and visited Moscow in 1814 and again in 1817. As a result of the latter trip he published the book *Journey from Moscow to Constantinople in the Years 1817-1818*, which is finely illustrated by drawings of his own.

In 1863 an uprising in Morocco against the Jews came to the attention of the venerable Sir Moses Montefiore. He decided to go to Saffi to advocate,



in person, the cause of his suffering people and set out with a large party, including his physician Thomas Hodgkin. Hodgkin, long curator of the museum and pathologist at Guy's Hospital, had, after he was sixty-five, given up practice and devoted himself to philanthropy. On conclusion of the affair in Morocco, the party went to the Holy Land, and there Hodgkin died, at Jaffa, in 1866. Hodgkin's account of the trip, however, was saved and published the same year under the title *Narrative of a Journey to Morocco in 1863 and 1864*. It is a delightful account, made more so by the excellent drawings of the author. Like Bright and Macmichael, Hodgkin had great ability as an illustrator.

Of slighter scope, but nevertheless of greater interest because of its contemporary nature, is a brief travel diary by the late Harvey Cushing, with illustrations, some in color, by his own hand.<sup>1</sup> Cushing, straight from four strenuous years as a surgical resident under Dr. Halsted at the Johns Hopkins Hospital, visited Le Puy in Auvergne in the summer of 1900, with a Yale classmate. He kept, as was his custom, a diary and to it added numerous sketches revealing, as Dr. John F. Fulton points out in the introduction to the published diary, Cushing's "unusual powers of observation, draftsmanship and humor." Some of the illustrations are water-colors that show remarkable talent. The sketches are characterized by a boldness of line and accurate perspective so notable in the operative drawings that fill his case-records from the time of his house-pupilage at the Massachusetts General Hospital in 1895<sup>2</sup> to the end of his surgical career. This charming account of the holiday visit to Le Puy is a worthy addition to the long list of travel books by doctors and, indeed, is one of the best.

#### REFERENCES

1. Cushing, H. *A Visit to Le Puy-en Velay: An illustrated diary*. 40 pp. Cleveland: The Rowfant Club (privately printed), 1944.
2. Viets, H. R. Notes on formative period of neurological surgeon. *Harvey Cushing's Seventieth Birthday Party, April 8, 1930*

### MASSACHUSETTS MEDICAL SOCIETY

#### DEATHS

COBB — Albert C. Cobb, M.D., of Marion, died March 21. He was in his seventy-seventh year.  
 Dr. Cobb received his degree from Albany Medical College in 1892.  
 A brother and five nephews survive.

LAWRENCE — Charles H. Lawrence, M.D., of Brookline, died March 13. He was in his sixty-third year.

Dr. Lawrence received his degree from Harvard Medical School in 1908. He served as lieutenant in the Army Medical Corps during World War I. In 1922, he was appointed to the Evans Memorial Institute for Clinical Research and became chief of the Endocrine Service there. He served as consulting physician to Jordan Hospital, Plymouth, Choate Memorial Hospital, Woburn, and Sturdy Memorial Hospital, Attleboro. He was physician-in-chief of the Endocrine Clinic at the New England Medical Center and associate professor of medicine at Tufts College Medical School. He was a fellow of the American College of Physicians and the American Medical Association, and a member of the Association for Study of Internal Secretions and the American Clinical and Climatological Association.

His widow, four sons and six grandchildren survive.

### NOTICES

#### BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in the Main Lecture Room of the Harvard Biological Laboratories on Wednesday, April 18, at 8 p.m.

#### PROGRAM

- The Sensitivity of Human Vision to the Spectrum. Dr. G. Wald.  
 Water and Electrolyte Exchange Between Blood and the Eye. Drs. E. Kinsey and M. Grant.  
 Composition of Typical Mexican Foods. Dr. R. S. Harris.

#### ALLERTON HOSPITAL

The next meeting of the Medical Staff of the Allerton Hospital, Brookline, will be held on Thursday, April 19, at 8:30 p.m. Dr. Albert E. Sloane will speak on the subject "Cataract in the Newborn."

#### NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

A meeting of the New England Ophthalmological Society will be held at the Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, on Tuesday, April 17, at 8 p.m.

Following the business meeting, Drs. V. Everett Kinsey and D. Morton Grant will speak on the subject "Physiology of Aqueous Humor Formation." An informal discussion by Colonel Derrick T. Vail on "Some Aspects of War Ophthalmology" will follow.

#### NEW ENGLAND ROENTGEN RAY SOCIETY

The next meeting of the New England Roentgen Ray Society will be held at the Harvard Club of Boston on Friday, April 20, at 8 p.m. Dr. E. Granville Crabtree will speak on the subject "Clinical Data on Some Pelvic and Ureteral Dilatations."

Interested physicians are invited to attend.

#### SOCIETY MEETINGS AND CONFERENCES

##### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 19

##### FRIDAY, APRIL 20

- \*9:00-10:00 a.m. Advances in Naval Medicine. Rear Admiral J. J. A. McMullin. Joseph H. Pratt Diagnostic Hospital.  
 \*9:00-10:00 a.m. Medical clinic Isolation Amphitheater, Children's Hospital.

10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Mallory Building, Boston City Hospital.

##### SATURDAY, APRIL 21

- \*10:00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

(Notices continued on page xix)

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## CURRENT TRENDS IN BIOLOGIC PRODUCTS\*

LIEUTENANT COLONEL ELLIOTT S. ROBINSON, M.C., A.U.S.†

THE following remarks on current trends in biologic products, not being based on a careful survey of current literature or opinion, represent only an expression of the impressions gained through some years of intimate contact with the manufacture of biologic products. Had there been more opportunity for painstaking study and preparation, the comments to be made might have undergone some alteration and doubtless would have greater value; but in these days, time for leisurely consideration has for many people joined those things that have essentially ceased to exist.

Current trends are discernible only against the background of what has happened in the past. For this reason, it is desirable not only to consider what is going on now and what was being done two or three years ago but to go farther back as well, if one is to see clearly how present thoughts and practices have developed and how they differ from those of earlier years. It will also be helpful if the large field of biologic products is divided into smaller portions, namely, antisera, — both prophylactic and therapeutic, — vaccines — both bacterial and viral — and toxoids.

The development of antisera, practically speaking, began with the discovery of diphtheria antitoxin in the 'nineties. The early antitoxins were not highly potent, and the doses required were relatively large. The quality too appears to have been more or less unreliable, and it was in the hope of providing more potent antitoxin that the Massachusetts Antitoxin Laboratory was established. For a number of years the chief improvement was in the direction of increasing the number of units of antitoxin per unit volume, thus reducing the volume required to provide a given dose. This was largely a matter of improvement in methods of toxin production and of immunization of horses.

The next step in development was the discovery that the antitoxic property is not associated with all the constituents of horse serum but only with the globulin fraction. This globulin can be separated

by treatment of the serum or plasma with ammonium or sodium sulfate, and the salt subsequently removed from the precipitated globulin by dialysis. At their best, these methods result in a reduction of volume of the original serum of the order of eight- to ten-fold and an increase in potency of the order of five-fold. This was an important development, for it permitted the administration of much larger doses and undoubtedly saved additional lives. It also led to some reduction in the incidence of serum sickness.

The next advance was not realized for a number of years, although it was discovered within ten years or less of the salting-out methods just described. This advance was the digestion method, brought to practical usefulness by Parfentjef, in which the plasma or serum is subjected to digestion by proteolytic enzymes. The antitoxic globulins are less susceptible to the action of the enzymes than are the other protein constituents of the serum, and their specific activity is not altered provided the enzymes are not allowed to act too long or too vigorously. The final product is often water-clear, and the activity per unit volume is high, permitting the administration of large doses in small volume. Serum sickness following the use of these products is infrequent.

The antibacterial serums have had a somewhat different course of development because of fundamental differences between the two varieties of serum. Prior to 1916, little had been accomplished in the development of antibacterial serums, but at about that time considerable success was achieved in the production of antimeningococcus serum and Type I pneumococcus antiserum. Both these were produced by the injection of horses with the appropriate bacteria. After a time, usually a number of months, the serum of the animals contained protective antibody in such concentration as to be useful therapeutically. Although antimeningococcus serum rapidly gained a recognized place as a useful therapeutic agent, antipneumococcus serum did not, because it was useful against only one type of infection, and also because the volume that it was necessary to administer practically limited its use to large and well-equipped hospitals.

\*An address given at the seventy-fifth anniversary of the Massachusetts Department of Public Health, Boston, December 6, 1944.

†Assistant professor of applied immunology, Harvard Medical School, and director, Division of Biologic Laboratories, Massachusetts Department of Public Health (on leave of absence).

In 1924, Felton published the first of a series of studies that marked the next stage in the development of antipneumococcus serum in particular and antibacterial serums in general. He worked on methods of antibody concentration, using sulfate precipitation and also precipitation by means of alcohol. The success of his work led to the widespread use of antipneumococcus serum, which was fostered by the development of statewide pneumonia-control programs. The history of these is too well known to warrant further discussion here, except to recall the leading role played by the Massachusetts Department of Public Health.

At the same time, Felton conducted extensive studies on methods of testing the potency of antipneumococcus serum. In the long run, this may prove to have been the more important contribution, for it focused attention on the difficulties involved in reasonably accurate bioassay of antibacterial serums, which in turn has led to more critical evaluation of the tests employed for other biologic products.

The next marked departure from previous practice was a change in the source of serum. With minor exceptions, the horse was for many years the main source of serums for human use, and this animal has several outstanding advantages for the purpose. Goodner in 1937 announced that more potent antipneumococcus serum could be produced in rabbits and proposed that these animals be substituted for horses. It was also claimed that the rabbit antibody (globulin) was of a smaller molecular size than the corresponding horse antibody, and that this characteristic should increase its ability to penetrate into pneumonic lesions. In my opinion, there has been no clear evidence that, unit for unit, rabbit serum gives better results than horse serum; but the switch to rabbits markedly increased the feasibility of producing serums for the less frequently occurring types of pneumococcal infection, and made possible the production and trial of other serums for which the demand is not great enough to warrant the use of horses.

Prior to the heyday of antipneumococcus serum, the intravenous administration of serums was not widely practiced, and little attention was paid to the occurrence of thermal reactions following intravenous serum therapy. These reactions, however, were of such frequency following the administration of antipneumococcus serum that they became a cause of grave concern, for they were often unpleasant and occasionally lethal. It now appears to be generally conceded that such reactions are produced by specific reaction-producing substances that are referred to as pyrogens. The exact nature of pyrogens does not seem to be clearly settled, although they are widely believed to be, and probably are, extraneous bacterial protein that is introduced into the serum in the process of manufacture. The method of introduction is sometimes obscure, but

scrupulous cleanliness and the use of pyrogen-free water in manufacturing processes seem to decrease markedly or to eliminate the occurrence of thermal reactions.

At the moment the current trend of antibacterial serums for therapeutic purposes is toward oblivion. The introduction of the sulfonamides and penicillin and their demonstrated effectiveness restrict the potential field of usefulness of serums largely to cases in which infection is due to drug-resistant bacterial strains or the patient is drug sensitive. This field is apparently small, much smaller in fact than some authorities feared during the early years of sulfonamide therapy.

Deserving of separate mention is the development of large-scale production of human blood and its fractions. It is important not only in itself but also because the methods developed will doubtless find application in the production of immune serums of animal origin. This development has been so recent, and is so well known that only the high lights and their probable effect on other biologic products need be mentioned here. The first step was the discovery that whole blood can be stored for limited periods for use in emergency transfusions. This was a justifiable but to some extent a wasteful procedure until it was learned that the blood cells can be discarded toward the end of the period of storage and the remaining plasma kept for a somewhat longer time. With the advent of war, the demand for plasma increased tremendously, but the difficulties of storing it in reasonably permanent form were considerable. These were overcome by storage as dried plasma, which was prepared by freezing the liquid plasma and removing the water by evaporation in vacuo. This has proved to be a highly satisfactory preparation for military use.

Just as only a relatively small portion of the serum carries antibodies, so too only a portion of the blood protein—in this case, the albumin—is of great importance in the treatment of shock. Exception can doubtless be taken to this opinion, but there was at any rate sufficient evidence to warrant the investigations undertaken under the direction of Cohn at Harvard to separate the albumin. These led first to the successful large-scale preparation of concentrated albumin solutions that in much smaller volume than plasma had an equivalent osmotic effect.

The methods used, with appropriate modification, have been employed for the separation of other serum-protein fractions. From the public-health standpoint, the most important is the gamma globulin, for this carries the naturally occurring antibodies. At present the most conspicuously useful of these is the antibody against measles. Extensive experiments have shown that human gamma globulin protects children who have been exposed to measles and can be used to modify the disease in such children. Other uses will doubtless be found, but this one alone is of considerable importance.

Let us turn our attention to the field of prevention, which, from the public-health viewpoint, is of greater interest, and first consider bacterial vaccines. Typhoid vaccine may be taken as an example, for it has been extensively studied and used and is of great importance to public-health and military medicine. Starting with its optional use in the British Army and its later adoption for compulsory use in the American Army in 1911, its value was conclusively demonstrated during World War I. The low incidence of typhoid fever in the Army during the years following the war made for a feeling of complacent acceptance of the value of typhoid vaccine, but this confidence was badly jarred by Grinnell's work at Harvard. He showed by experiments on mice and with human volunteers that the Rawlings strain ordinarily used for vaccine production was not particularly effective in producing active immunity in the mice or protective antibody in the human volunteers. This failure was associated with a loss of virulence of the Rawlings strain, probably the result of prolonged cultivation; for vaccines made from recently isolated typhoid strains were definitely superior both in mice and in human subjects. Moreover, a virulent Rawlings strain produced by mouse passage was of distinct immunizing value when used for vaccine production. Grinnell's recommendation of the use of a virulent strain was promptly adopted by the Massachusetts Antitoxin and Vaccine Laboratory. His experiments were confirmed on a large scale by the Army Medical School. His recommendations have for some time been generally accepted, and have been incorporated into current practice with respect to most bacterial vaccines.

A useful bacterial vaccine must be effective and must be safe. Effectiveness seems to be most nearly achieved when the bacterial antigen is present in the form found in the living bacterium. The use of a live bacterial vaccine violates the requirement of safety, so that methods of killing the bacteria must be used that will alter as little as possible the character of the bacterial antigen. For many years heat has usually been relied on for this purpose, although chemicals have been employed more or less widely. Recently irradiation with ultraviolet light has been studied, and to some extent this appears to be more promising than any other measure yet devised. Regardless of the method employed with whole-organism vaccines, it is believed that no more than the minimum dose effective for killing should be used; and even this may be enough to affect the antigen more or less deleteriously.

An entirely different approach to the problem of vaccine production is the attempt to isolate the antigen from the bacterial cell by chemical methods. This is undoubtedly the method most to be desired, for theoretically it provides pure antigenic substance free of extraneous material, and permits determination of dosage in terms of weight of the pure sub-

stance without the necessity for resort to more or less cumbersome bioassays. Furthermore, the pure antigens are probably more stable, at least in concentrated or dry form, than are the corresponding bacterial suspensions. Success in isolating more or less pure antigens has been attained in the case of the typhoid bacillus and, more conspicuously, with the pneumococcus, although in neither instance has the antigen been widely adopted for use. It seems likely, however, that further development of vaccines will follow along this line.

It might have been appropriate to begin the discussion of vaccines with those made from viruses, since historically a virus vaccine — that protecting against smallpox — was the first to be generally used. This particular vaccine, however, has undergone very little change in recent years, and except for relatively minor technical improvements is made essentially as it was forty or more years ago. Smallpox vaccine is obtained by the inoculation of the skin of calves with vaccinia virus and subsequent harvesting of the resultant vesicles. Rabies vaccine is obtained by propagating the virus in rabbits and removing the spinal cords, rich in virus, when the animal shows pronounced symptoms of the disease. Other viruses, too, could for many years be propagated only by inoculation of susceptible animals; and if vaccines were to be made they must represent suspensions of the appropriate animal tissues. For some of the virus diseases, such as chicken pox, vaccination would hardly seem worth while even if it were available, for these particular diseases are usually mild; and for others, no suitable susceptible animal is known.

The most striking advance in recent years was the discovery that many viruses can be grown in chick embryos. The most favorable site and time of inoculation and the part of the embryo in which the virus develops most luxuriantly depend on the particular virus. Although many viruses and rickettsias can be grown in this way, some cannot, so that it is still not possible to develop a vaccine against any and every type of virus. The most extensively used of the chick-embryo vaccines are those for yellow fever and for louse-borne (epidemic) typhus fever. Both these vaccines have been used on a large scale by the Army as well as in civilian groups, and the results have been excellent. There is also in preparation a vaccine against influenza, Types A and B, which it is hoped to have available for military use in the event of an outbreak of influenza. It is to be expected that similar vaccines against other diseases due to viruses will come into more or less extensive use, for there are strong indications that they will have value. Some of these diseases, such as St. Louis encephalitis, are relatively rare, so that vaccines against them may not be widely used even if they become available.

One thing that may curtail the use of vaccines derived from chick embryos is the possible develop-

ment of egg sensitivity in persons inoculated with these vaccines. The possibility of its occurrence has been noted and a case report has been published, but there has so far been little in Army experience to indicate that this is a serious danger. It should not be overlooked, however, that the danger might be increased if the use of such vaccines became general or were extended to the younger age groups.

Another group of prophylactic biologic products deserving of mention comprises the toxoids. Bacterial toxins are ordinarily too poisonous to permit their use as antigens in human beings, the permissible doses being too small to be effective. This is conspicuously true in the case of diphtheria and tetanus. It is relatively easy to destroy their toxicity with formaldehyde without any great destruction of antigenic efficiency. Diphtheria toxoid prepared in this way came into general use in this country in about 1930. The fact that three doses were ordinarily required to produce satisfactory levels of immunity led to the adoption of toxoid precipitated on alum. Not only is such a precipitate a more effective antigen than the unprecipitated toxoid, but the process also eliminates extraneous constituents of the basic material.

Although toxoids are in general reasonably free from undesirable side reactions, diphtheria toxoid and, less frequently, tetanus toxoid may give rise to marked but transient local or general reactions. It has also been found that tetanus toxoid may give rise to reactions of the anaphylactic type, but this difficulty was definitively traced to the use of certain peptones in the medium in which the toxin was produced. These reactions stimulated interest in the use of mediums of known chemical constitution for toxin production, for such mediums contain only substances of relatively low molecular weight and are therefore nonantigenic. The first successful step in this direction was the adaptation by Pappenheimer at the Antitoxin and Vaccine Laboratory of the medium devised by Mueller at Harvard for the growth of diphtheria bacilli. This medium has been in routine use for several years and has yielded high-grade toxin of uniform quality. Equally successful results have not been obtained with tetanus toxin production, but advances have been made. It is undoubtedly in this direction that further improvements will follow.

An outgrowth of the production of diphtheria toxin on a medium of known composition was the isolation of essentially pure diphtheria toxin by Pappenheimer. This was previously done by Eaton, but there was uncertainty of his complete success because of the complex nature of the medium. Actually, Eaton's preparations were excellent. The use of toxoids made from pure toxins has not as yet been practically applied, for the ordinary commercial preparations of both diphtheria and tetanus toxoid have been in general quite satisfactory; but the possibility of using pure preparations is one that may in the future become of increasing importance.

One other trend in current practice is worth mentioning. So many definitely useful prophylactic agents are now available that innumerable injections would be given if advantage were taken of all of them. Therefore a number of combined preparations have been proposed, and several have been more or less generally adopted. Diphtheria and tetanus toxoid together or mixed with pertussis vaccine have been employed in pediatric practice, and a combination of tetanus toxoid with typhoid-paratyphoid vaccine has found some favor for military use. Opinion has at times been divided concerning the efficacy of antigens simultaneously administered, but there seems to be little difference between the results from giving them separately and giving them together, at least when the number of antigens is limited to two or three. The use of such combinations may be expected to increase.

Since this is a celebration of the fiftieth anniversary of the Antitoxin and Vaccine Laboratory as well as of the seventy-fifth anniversary of the Department of Public Health, I should like in closing to call attention to the fact that the laboratory has played a not inconsiderable part in shaping the trends that have been described. This has been possible largely because of the close association of the laboratory with the other scientific institutions in Boston, notably with the Harvard Medical School. Nowhere in this country is there the favorable situation existing here, with a state laboratory actively engaged in the manufacture of biologic products located so close to first-rate medical schools. Let us hope that the future will see the continuance of this mutually profitable association.

## ENGINEERS AND ENGINEERING IN THE MASSACHUSETTS STATE BOARD OF HEALTH\*

GORDON M. FAIR†

CAMBRIDGE, MASSACHUSETTS

THE story of public health in its modern implications, like that of other great social reforms, is the story of great men whose convictions and leadership, wisdom and toil, temporary failure and ultimate success fashioned a pattern of public opinion that could not be denied and that has left its imprint on a century of human existence.

The public-health movement as it is seen today had its roots in the Industrial Revolution of the nineteenth century. Industry, the child of scientific discovery and invention, created the opportunity for mass employment. In the early stages of industrial development, limitations on the transmission of power and the need for a nearby labor market forced the herding together of people in houses that clustered about the factories. To meet the rapid influx of workers, these mushrooming communities often could not expand their facilities fast enough to satisfy new and often frightening sanitary needs. In particular did the need for more abundant distribution of water, for more effective disposal of human wastes and for more adequate housing force itself on the attention of thoughtful men whose duties, associations or interests brought them into contact with the suffering of the masses of the people.

We can understand, therefore, why engineers were engaged from the very beginning in the modern public-health campaign. The example for so doing was set in England during the great sanitary awakening of the middle-nineteenth century. There Sir Robert Rawlinson was employed by the General Board of Health in 1848 as superintendent inspector, and in this capacity conducted the engineering studies necessary for the construction of sanitary works in growing industrial Britain. The real genius of British public health and the originator of many of its engineering advances, however, was Sir Edwin Chadwick. There is no gainsaying that the main threads of public-health progress in Great Britain tie back to him. In the United States, these threads, too, can be traced to a single man, Lemuel Shattuck, like Chadwick neither a physician nor an engineer, but an enthusiast for sanitation. What Shattuck<sup>1</sup> reports a London periodical of December, 1849, as saying about Chadwick would seem to apply equally well to Shattuck himself:

He was not a man of varied or profound attainments, nor distinguished by any extraordinary brilliancy of intellect. But he was remarkable for his sagacity in extract-

ing from masses of detail the master facts, and bringing these to bear for the elucidation of a master thought. He would confront, undaunted, any amount of intellectual labor, exploring mountains of blue books and statistical returns till he had fully ascertained and brought to light their true riches.

Shattuck's "Report of a General Plan for the Promotion of Public and Personal Health" was presented to the General Court of Massachusetts on April 25, 1850. His conclusions were based on intensive studies of the sanitary movements abroad and at home. Because of the similarity in social background of the two countries, British experience, above all, influenced Shattuck's plan for a sanitary survey of the Commonwealth. Among the measures advocated in this plan were the establishment of a general board of health, composed so far as practicable "of two physicians, one counsellor-at-law, one chemist or natural philosopher, one civil engineer, and two persons of other professions or occupations; all properly qualified for the office by their talents, their education, their experience and their wisdom."<sup>2</sup> Two reasons were given why the members should not be selected exclusively from one profession. In the first place, Shattuck anticipated that numerous questions, requiring a knowledge possessed by different professions, would be presented for discussion and decision. Second, the promotion of public health, in Shattuck's mind, was a matter that concerned every profession and every person. The services of medical men were indispensable, but the services of other professions, and of every person in their respective spheres, must be put in requisition before reform could be complete.

The civil-engineer member of the proposed board, Shattuck<sup>3</sup> suggested, should possess "competent knowledge to determine the best methods of planning and constructing public works, and the best architectural sanitary arrangements of public buildings, workshops and private dwelling-houses."

Although nineteen years elapsed before the Massachusetts State Board of Health was established and five more before John C. Hoadley, of Lawrence, was appointed engineer member of the board, this recommendation of Lemuel Shattuck's seems to be the American wellspring of engineers in public health. About Hoadley, who served from 1874 to 1882, it is known that he began his career as a civil engineer on the enlargement of the Erie Canal and was later placed in charge of locating, constructing and installing textile mills in Massachusetts. In the course of time, his work with textile machinery turned him away from the field of civil engineering to that of mechanical engineering, in

\*An address given at the seventy-fifth anniversary of the Massachusetts Department of Public Health, Boston, December 6, 1944.

†Abbott and James Lawrence Professor of Engineering, and Gordon McKay Professor of Sanitary Engineering, Harvard University.

which he became expert. This shift in interest may explain why he did not provide the engineering leadership that he might have exerted in the new board. An examination of the scientific articles and reports published in the regular series of annual reports shows but two articles over Hoadley's signature. During the same years the medical members of the board were, indeed, more active in discussing engineering topics than was the engineer member himself. The board, however, employed as consultants some of the outstanding civil engineers of the period, in particular James P. Kirkwood, who was the first American engineer to build a filtration plant for water purification, and E. S. Cheshbrough, who was to become celebrated for his designs of some of the great sewer systems in the United States.

Investigations of the board that involved problems of chemistry were generally assigned to Professor William R. Nichols, of the Massachusetts Institute of Technology. Nichols, thereby, became the pioneer American water chemist. That the services of a chemist would be needed had been foretold, too, by Shattuck,<sup>3</sup> who wrote: "Many questions relating to the influence of the elements on the production or prevention of disease may require the special investigation of an experienced chemical philosopher, and this important branch of science should be ably represented at the Board."

It is a happy coincidence that in 1869, the year in which the Board of Health was organized, there was appointed as chief engineer of the Essex Company in Lawrence one Hiram F. Mills, then thirty-one years of age, for as we shall see the destiny of each was to be deeply influenced by the other. Mills was one of the first graduates of an American school of engineering, the Rensselaer Polytechnic Institute. He had worked with Kirkwood and also with Charles S. Storow and James B. Francis, chief engineers respectively of the Essex Company in Lawrence and the Merrimack Manufacturing Company in Lowell. These men were the leaders of hydraulic engineering in the New World. With the examples of Francis and Storow before him, Mills early determined to prepare a treatise on hydraulics, and set about gathering the necessary experimental information. When he became chief engineer of the Essex Company, which owns the dam and canal on the Merrimack River at Lawrence and controls the water needs of the manufactories, the opportunity presented itself to build a laboratory in which he could and did conduct his contemplated hydraulic researches. John R. Freeman, himself to become an engineer of distinction, was Mills's principal assistant for many years and has commented on "the rare devotion of Mr. Mills to the search for scientific truth and the deep insight, the untiring earnestness, and the consummate skill with which he carried on observations."<sup>4</sup> This talent for research Mills carried with him when he was appointed a member

of the State Board of Health in 1886, a fact that is probably responsible for the remarkable service that engineers, chemists and biologists were able to perform for the Commonwealth under his leadership. Of Mills's association with the board, which had been reorganized in 1886 under the chairmanship of Dr. Henry P. Walcott, Freeman writes as follows:

His profound interest and zeal as an investigator were then awakened to the importance of advancing scientific knowledge in matters of purification of public water supplies and of prevention of stream pollution, and for about twenty-eight years this work of one kind and another for the Massachusetts Board of Health, for which he received no pecuniary compensation, absorbed a majority of his time, to the neglect of his earlier investigations in hydraulic science. . . .

Later, when in partial retirement long after he had passed three score and ten years he resumed this earlier task, failing strength prevented his continuing these hydraulic investigations or discussions on the scope originally planned.<sup>5</sup>

Mills at the age of eighty years told Freeman with much feeling that he "had put off this work too long." Nevertheless he collected his many notes and from day to day, up to his eighty-fourth year, worked over them patiently and steadfastly as many hours as his strength would permit, declining the assistance of younger eyes and hands. Although he did not complete his notes for publication, they were made available to the profession by Karl R. Kennison,<sup>4</sup> now chief engineer of the Boston Metropolitan Water Supply, as a memoir of the American Academy of Arts and Sciences in 1924, three years after Mills's death.

But let us return to the memorable year of 1886. Along with the reorganization of the State Board of Health there was passed in that year a very important act of the Legislature, entitled "An Act to Protect the Purity of Inland Waters."

Briefly, this act placed in the hands of the State Board of Health the general oversight and care of all inland waters, directed that examination of the waters be made to ascertain whether they were adapted for use as sources of domestic supply or likely to imperil the public health, and that recommendations be given as to the prevention of pollution. Authority was given to employ expert assistance, and to conduct experiments to determine the best practicable methods of purification of sewage or disposal of manufacturing refuse. The Board was also ordered to give advice to cities and towns, corporations and individuals as to sources of water supply and methods of sewage and refuse disposal, without expense to persons advised. Provision was also made for the submission to the Board of all plans and schemes in relation to water supply and the disposal of drainage or refuse, for its advice. And, finally, the Board was ordered to bring to the notice of the attorney general all instances of violation of the laws respecting the pollution of water supplies and inland waters.<sup>5</sup>

To carry out the provisions of this act, an engineering department was created in the State Board of Health, with Joseph P. Davis as consulting engineer, Frederick P. Stearns as chief engineer and X. H. Goodnough as assistant engineer. Davis had been chief engineer of the Cochituate Water Board,

the City of Boston and the Boston Main Drainage System, and so brought to his consulting work a wealth of experience. Stearns directed the Engineering Department during its formative years, and would probably not have relinquished his position to become chief engineer of the Metropolitan Water Board, which constructed the Wachusett water supply for the Boston Metropolitan District, had this enterprise itself not been one of the great projects of the State Board of Health. Goodnough succeeded Stearns in 1895 and, on his retirement in 1930, passed on the reins of the Engineering Department to the present incumbent, Arthur D. Weston.

Along with the development of an engineering staff, the Act to Protect the Purity of Inland Waters had made available funds for the systematic analysis of water. This permitted drawing into close association with the engineers a notable group of chemists and biologists, some of whom were on the faculty of the Massachusetts Institute of Technology, in whose laboratories the analytical work was performed until 1896, when a water laboratory was set up in the State House. In order to conduct experiments to determine the best practicable methods of purification of sewage or disposal of manufacturing refuse, Mills placed at the disposal of the State Board of Health his hydraulic laboratory at Lawrence, about which we have already heard. This laboratory was renamed the "Lawrence Experiment Station" and has continued its useful existence ever since. As a laboratory for sanitary research, this station was the first of its kind, and its influence on the progress of sanitary engineering cannot be overestimated. To staff the station, Mills drew heavily on young graduates of the Massachusetts Institute of Technology who had come under the influence of teachers who were then active in the chemical and biologic investigations of the State Board of Health.

Thus was initiated a decade of sanitary investigation the like of which has never been seen again in Massachusetts or anywhere else in the world. With the support of Dr. Walcott, and unified in their objectives by Mills's broad conception of what was needed in the task ahead, the Engineering Department, the Water Laboratory and the Experiment Station collaborated with imagination and zeal to initiate great engineering enterprises, lay the foundation for sanitary analysis and establish the experimental method as a means for determining the scientific and economic basis of public sanitation. The association of young men in this great adventure in sanitation appears to have been mutually so inspiring that there was to be hardly a man among them who did not make a significant contribution to the advancement of knowledge during his stay with the board and who did not, as well, make a name for himself in later life.

A list of these men would include among others the names of Thomas M. Drown, chemist, successor to Professor William R. Nichols at the Massachu-

setts Institute of Technology and later president of Lehigh University; William T. Sedgwick, biologist, later professor of biology at the Massachusetts Institute of Technology; Allen Hazen, engineer investigator, later one of America's greatest practitioners; George W. Fuller, chemist, who later at Louisville, Kentucky, laid the foundation for rapid sand filtration; Gary N. Calkins, biologist; later professor of protozoology at Columbia University; Edwin O. Jordan, bacteriologist, later professor of bacteriology at the University of Chicago; and Harry W. Clark, chemist, later director of the Water Laboratory and the Lawrence Experiment Station.

Notable among the great engineering enterprises of the group were the investigations that produced the Metropolitan Sewerage System of Boston, the Metropolitan Water Supply of Boston and the Charles River Basin, public works that satisfied the highest standards of engineering achievement and that continue to serve their intended function with success and distinction.

Many of the early studies of water purification and sewage treatment at the Lawrence Experiment Station are counted among the classics of sanitary engineering literature. Some of them, in fact, were so fundamental and so well conceived that they have continued to be reprinted in books on sanitary engineering for half a century. The Lawrence Experiment Station eventually became a mecca for engineers, chemists and biologists interested in the purification of water, the treatment of sewage and industrial wastes and the control of stream pollution. The visitors' book of the station is a veritable "Who's Who in Sanitation throughout the World."

The fundamental organization of state sanitation initiated in 1886 has continued up to the present time. The Department of Public Health has undergone two major reorganizations, those of 1914 and 1919, but the Engineering Division itself has pursued the even tenor of its ways with little deviation from its original aims and objectives except as expanding interests have brought new and varied problems to its staff for solution. In the course of time, the Engineering Division has built up a record of service and a background of legal justification that are unique in public enterprise.

The co-operation between the Engineering Division, the Water Laboratory and the Lawrence Experiment Station, which had been so fruitful during the early years of their existence, was allowed to become less close for a number of years. This worked particularly to the disadvantage of the Experiment Station, which lacked the challenge of engineering problems to be solved in practice. During this period some of its investigations appear to have been less well conceived and executed, as well as less productive of useful results. This situation was remedied some years ago, and there are signs that the station is on the way to recapture the fame and



usefulness that it acquired during its first score of years.

The powers of the Division of Sanitary Engineering have been advisory, in accordance with the general policy of the Department of Public Health. Only in times of severe stress has the "grammar of common sanitary legislation acquired the novel virtue of the imperative mood."<sup>6</sup> In this has probably lain the greatest incentive of the division for service. Throughout its existence, the counsel of the division has been sought as originally contemplated, and the record of applications for advice is one of steady growth. The construction of sanitary works in the Commonwealth has borne a direct relation to the activities of the division. This is exemplified by the progressive introduction of public water supplies. Prior to 1869 there were only seventeen such supplies in Massachusetts; by 1890 this number had increased to one hundred and thirty-eight; and by 1940 the 256 public water supplies of the Commonwealth served no less than 97 per cent of its total population. That these constructions were justified is shown by the declining annual death rate from typhoid fever. In 1873 this rate was 89 per 100,000 population; by 1890 it had dropped to 37, and by 1940 to 0.2.

Such is the story of engineering and its ancillary services within the Massachusetts State Board of Health. Needless to say, the work done has paid for itself over and over again in lives saved and sickness avoided, as well as in the general comfort and well-being of the people of Massachusetts. The influence of this pioneer engineering organization in a public-health department, however, has extended far beyond the borders of the State and, indeed, beyond the boundaries of the Nation. The published reports of the board became one of the most important sources for sanitary information, and young engineers trained in the Engineering Division carried its spirit and its methods with them when they left to join or organize the engineering divisions of other health departments, to take part in the design and construction of great sanitary works or to become teachers of sanitation in schools of engineering and schools of public health.

When Hiram Mills followed the injunctions of Lemuel Shattuck in his attack on the fundamental problems of environmental control by putting in requisition the services of other professions in their

respective spheres, he created, in fact, a new and important discipline of public health as well as engineering and a career to be embraced by young engineers who, like Chadwick and Shattuck, could become enthusiasts for sanitation. Collaboration in sanitary research for the solution of basic engineering problems established above all the desirability of equipping engineers with a knowledge of chemistry and biology, and the study of these subjects has since become a heritage of sanitary engineers in America. The challenge that engineers could build disease or health into their works could either be turned aside by relegating responsibility for public-health decisions to other professions—as was done and has very largely continued to be done abroad, and I may add with less success—or it could be accepted by acquiring an adequate fund of information to be able to evaluate the public-health factors concerned. The engineers of Massachusetts chose to shoulder the responsibility themselves and so to play a significant part in the sanitary control of the human environment by engineering means.

After reviewing these contributions of Massachusetts to public health, I can find no more fitting expression for my own admiration of her accomplishments than is suggested by the last paragraph but one of Lemuel Shattuck's report wherein, after enumerating the many ways in which Massachusetts has stood for social progress, he says:<sup>7</sup>

For these and very many other useful and honorable deeds, which might be specified, she has been named, by distinguished men of other states and countries, "the forefather's land," "the moral state," "the enlightened state," "the patriotic state," "the philanthropic state," "the leading state," "the pattern state," "the noble state," "the glorious old Bay State."

And may I be permitted to add, "the birthplace in America of public health and with it of the engineer in public health."

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## MEDICAL PROGRESS

## THE CLINICAL IMPORTANCE OF THE RH BLOOD TYPE\*

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IN the five years that have elapsed since the Rh factor in human red cells — better known as the Rh blood type — was first discovered, there has been a steadily increasing volume of literature on this subject. In the past two years alone, more than two hundred such articles have appeared in medical journals. Many of these have been concerned with the laboratory aspects of Rh typing, Rh antisera, nomenclature and the heredity of the possible subtypes of the Rh factor, thus suggesting to some physicians that this new field has in it relatively little of clinical value. On the other hand, many more articles have described particular patients and have elaborated on and drawn sweeping conclusions from single case reports of transfusion accidents, of pregnancy difficulties or of anemia in newborn infants. As a result of the latter, the idea has grown that the Rh factor and Rh incompatibility account for many blood transfusion reactions, for most late stillbirths or even early abortions and for all jaundice and anemia in early infancy.

The truth concerning the practical clinical importance of the Rh blood type lies somewhere between the extremes of these two points of view. There now is sufficient and convincing proof of the role of this new blood type in hemolytic transfusion reactions, in certain complications of pregnancy and in neonatal anemias. It is not valid to assume that it accounts for almost all such cases, especially those in which clinical data are incomplete and laboratory confirmation is absent.

In reviewing case reports and experiences with Rh typing and Rh agglutinin detection in the past, some reasons for misinterpretation and confusion become apparent. At first, serum produced experimentally in guinea pigs or weak varieties of human anti-Rh serum were chiefly used for Rh determinations. Because of the poor avidity (slow development of agglutination) and low potency of such serums, weak reactions were often obtained. Also it was not generally appreciated that blood cells vary in their agglutinability with anti-Rh serum, some exhibiting rather weak clumping. In addition, the agglutination reaction tends to become weaker as the cells are stored, even for as little as one or two days. Finally, vigorous shaking of the clumped cells may sometimes break up the agglutinates and thus yield false negative results. The

use of avid, potent serums has produced accurate and valid results.

The difficulties of detecting Rh sensitization by demonstrating anti-Rh agglutinins also were not fully appreciated. The resulting failures of laboratory confirmation of Rh incompatibilities and Rh sensitization detracted from the value of clinical material. Also, since relatively few laboratories were equipped with Rh typing serum and technical experience in demonstrating Rh agglutinins, the patients thought to be suffering from sensitization to the Rh factor could not always be studied in their own hospitals, and valuable clinical observations were not correlated with the laboratory data.

Now that potent and rapidly acting Rh typing serums are more readily available, that technics for testing for the Rh factor and for evidences of Rh sensitization are better understood and standardized and, finally, that clinical correlation on much larger numbers of patients is possible, the practical importance of the Rh blood factor should be clearly evident. The basis for this summary of present knowledge is a critical review of the readily available literature on the subject and the large number of experiences and the large volume of data gathered in the past three years in a single laboratory.‡

## THE RH FACTOR

The Rh factor in human blood cells, or the Rh blood type, was first discovered by Landsteiner and Wiener<sup>1</sup> in 1940 as the result of their experimental studies of agglutinins developed in guinea pigs and other experimental animals against the red cells of the rhesus monkey. One of the agglutinins was found to act on bloods of 39 of 45 human subjects. The agglutininogen was therefore named the "Rh factor" because it had been found first in the cells of the rhesus monkey. Human cells agglutinated by the anti-rhesus (anti-Rh) serum were designated as Rh+ (Rh positive), and those not agglutinated as Rh- (Rh negative).

The following year the same workers<sup>2</sup> proved that the Rh factor was present in the red cells of about 85 per cent of the white population (Rh+ persons) and absent in about 15 per cent (Rh- persons). Subsequently, human anti-Rh serums having a wider range of reaction were used to type larger groups of

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‡The Blood Grouping Laboratory was formed in 1942 under the sponsorship of the Boston Lying-in Hospital, the Children's Hospital, the Massachusetts Memorial Hospitals and the Massachusetts General Hospital, for the purpose of performing accurate blood grouping, Rh typing and anti-Rh determinations on the patients of these hospitals and of collecting and preparing Rh typing serum for use locally as well as in outside hospitals needing it. At present, the laboratory averages five hundred Rh tests and fifty anti-Rh determinations per week.

individuals of different racial background. It seems to be well established now that slightly more than 87 per cent of the white population is Rh+, and less than 13 per cent is Rh-. In typing persons of the Negro race, it has been found that about 90 to 95 per cent are Rh+,<sup>3</sup> and in the Chinese and the American Indian 99 per cent are Rh+.<sup>4-6</sup> Numerous excellent papers have reported on the racial distribution, the inheritance and the subtypes of the Rh factor.<sup>7-20</sup> As a general rule, sensitization to the Rh factor, with the exception mentioned below, occurs only in Rh- individuals. Such persons become immunized against this Rh agglutininogen by means of one or more transfusions of Rh+ blood, or such women by one or more pregnancies involving Rh+ infants.

The exception to the above statement, that sensitization to the Rh agglutininogen occurs only in Rh- subjects, has been demonstrated in about half a dozen cases by us and by Wiener.<sup>21</sup> Occasionally an Rh+ individual may become sensitized and develop immune bodies against an Rh agglutininogen. This has been found to be dependent on the presence of subtypes of the Rh factor, several of which have been identified by Wiener and by Race and Taylor. In these rare cases, sensitization of an Rh+ woman whose blood belongs to one subtype of the Rh factor (as, for example, Rh<sub>1</sub> or Rh<sub>2</sub>) occurs through pregnancy or, more frequently, after transfusion with Rh+ blood of her husband whose blood cells belong to another subtype. Agglutinins may then develop against the Rh fractions foreign to the woman. Subsequently, transfusion reactions or hemolytic disease in a fetus having the same Rh fraction as was used for the transfusion may occur. Such cases, which may be confusing and difficult to resolve by ordinary Rh testing, are fortunately extremely rare. Much more frequently, Rh determinations of persons involved in intragroup hemolytic transfusion reactions show that the recipient of the transfusion is Rh-, and the donor Rh+, and that previous transfusions of unknown or definitely Rh+ blood caused the immune response. Or, in cases of erythroblastosis fetalis the mother is Rh- and the father and child Rh+, with antibodies in the mother against the Rh factor developing as the result of one or more previous pregnancies involving an Rh+ infant.

#### INTRAGROUP TRANSFUSION REACTIONS

As mentioned above, the typical case of transfusion reaction due to Rh sensitization involves an Rh- recipient who received two or more transfusions of Rh+ blood over an interval of time sufficient to permit the development of antibodies. A typical case history follows.

**CASE 1.** *Hemolytic reaction following repeated transfusions of Rh+ blood.* A 26-year-old woman, with recurrently severe anemia secondary to menorrhagia, in 1939 received a 500-cc. transfusion from her husband (Donor 1) and 3 days

later a 600-cc. transfusion from her brother-in-law (Donor 2); neither was followed by a reaction. Six months later she was given another transfusion from Donor 1, which was interrupted at 300 cc. because of pain in the flanks and dyspnea; subsequently hemoglobinuria developed. Two days later she received a 600-cc. transfusion from her sister (Donor 3), without reaction. One week later, another transfusion from Donor 2 was begun. This was interrupted after only 200 cc. because of severe dyspnea and signs of shock; anuria and jaundice appeared within 24 hours. One day later she received a 600-cc. transfusion from her brother (Donor 4), without reaction. In 1941, she was given two transfusions, totaling 1300 cc., from professional donors (Donors 5 and 6), without reaction.

Blood typings were as follows: patient, Group 0, Rh-; Donor 1, Group 0, Rh+; Donor 2, Group 0, Rh+; Donor 3, Group 0, Rh-; Donor 4, Group 0, Rh-; Donor 5, Group 0, Rh-; and Donor 6, Group 0, Rh-. Anti-Rh agglutinins were eventually demonstrable in the patient's serum.

This girl required multiple transfusions because of repeated blood loss over a period of more than two years. The first two transfusions, from her husband and from his brother, were given with no untoward results. Six months later, however, another attempted transfusion, again using the husband as donor, produced signs of incompatibility. An attempted transfusion from the second donor produced even severer signs of hemolytic reaction. In the interval, transfusions from the patient's own blood relatives were uneventful. The following year, two transfusions from professional donors, chosen because of their Rh- quality, were administered with no reaction. This patient's course of transfusion reactions was indeed puzzling, since homologous group blood produced serious reaction after a former successful transfusion from the same donor. Only by differentiation on the basis of the Rh testing was the cause of the difficulty revealed.

Another patient whose history is typical of that of many cases of chronic anemia is illustrated by the following case.

**CASE 2.** *Hemolytic reaction following repeated transfusions of Rh+ blood.* A 42-year-old man with aplastic anemia was given three transfusions within a week, following which his hemoglobin level rose from 35 to 80 per cent. Three months later, he received two more transfusions in rapid succession. These were followed by chills and fever. His hemoglobin level rose from 45 to only 50 per cent. After a week, another transfusion was given; this produced a severe chill, fever, hemoglobinuria and, the next day, mild jaundice. The hemoglobin fell to 30 per cent after this treatment.

Blood studies revealed that the last donor used was Group 0, Rh+. The patient was also Group 0 and apparently Rh+, since some clumps of cells were visible, grossly, in the test of his red cells with anti-Rh serum. Microscopically, however, it was evident that only a few red cells were strongly clumped and that most of them were free and unagglutinated. This strongly suggested that the blood cells were mixed. An anti-Rh test of the patient's serum was negative.

Three transfusions, from Rh- donors, were given with no untoward reaction, and the hemoglobin rose from 30 to 85 per cent. Two weeks later, the patient was retyped, and his cells proved to be Rh-. Anti-Rh agglutinins were then demonstrable in his serum. Subsequently, more than twenty transfusions of Rh- blood were administered, with no untoward reactions.

This patient responded favorably to three transfusions, given within a week, of compatible, homologous blood. Three months later, two transfusions of similar blood were given with the development

of chills and fever and the failure of a satisfactory hemoglobin response. About two weeks later, another transfusion of satisfactorily cross-matched blood produced even more serious symptoms of a hemolytic transfusion reaction, with chills, jaundice, hemoglobinuria and a fall in hemoglobin level. At that time, blood grouping and typing proved that the last donor used was Rh+; gross examination of the test tube containing the patient's cells and anti-Rh serum showed some clumping, which suggested an Rh+ reaction. Microscopic examination, however, showed that there were few clumped cells and that most of the cells were unagglutinated. This suggested that the patient's blood was Rh—, with some Rh+ cells from the donor still circulating in his system and agglutinable by the testing serum used. The patient's own serum failed to show any anti-Rh agglutinins. Because of the probability that the patient was Rh—, three transfusions of Rh— blood were given with no untoward reaction and with a satisfactory response in hemoglobin level. Two weeks later, by which time the donor's cells that originally caused the reaction were presumed to have been entirely destroyed, the patient's blood was retyped and was found to be Rh—. The serum of the patient showed the development of anti-Rh agglutinins, which had had a chance to reaccumulate in the elapsed time. Subsequently, this patient received numerous transfusions of Rh— blood with no untoward reactions.

This type of case is not infrequent in a patient who requires multiple transfusions. At first, there may be benefit from the infused cells, but subsequently more and more signs of untoward reactions develop and the treatments become less satisfactory. Because of this, it was assumed that patients with chronic or recurrent anemia from repeated blood loss, leukemia, aplastic or hemolytic anemia were peculiar in their tendency to suffer transfusion reactions. It is now realized that many of these patients probably had been sensitized by the use of blood containing an agglutino-gen foreign to the recipient, and the development of agglutinins against this blood type interfered with future use of similar blood. With precautions, not only for Rh type but also for the subtype of the A blood group, such reactions in patients requiring multiple transfusion over a long period of time can now be minimized.

That such agglutinins may remain in the recipient's system for many months or even years has now been demonstrated in other patients.<sup>22</sup> One patient studied by us, who had received several transfusions eight years before and two transfusions twelve years before, developed signs of a hemolytic transfusion reaction when retransfused with Rh+ blood.

The occasional brief period that may elapse between initial stimulation from an Rh+ transfusion and the development of anti-Rh agglutinins is illustrated in the following case.

**CASE 3. Hemolytic reaction following repeated transfusions of Rh+ blood.** A 14-year-old boy with hemophilia suffered recurrent bleeding from the gums requiring four transfusions on four successive days. These produced an increase in hemoglobin level from 25 to 60 per cent. One week after the first transfusion, and only 4 days after the last, two more transfusions were necessary because of severe hemorrhage. After the second, the patient complained of feeling chilly, had abdominal pain, passed a small amount of bloody urine and then no further urine for 24 hours. His hemoglobin rose from 50 to only 60 per cent. The next day there was slight jaundice.

Blood typings showed that the last donor was Group A, Type M, Rh+. The patient was Group A, Type MN, apparently Rh+, since gross clumping was visible in the test tube. Microscopically most of the cells were unagglutinated. This suggested a mixture of positive and negative blood in the patient's circulation. His serum showed no anti-Rh agglutinins.

The next day two more transfusions were administered from donors who were Group A, Type N, Rh—, with no untoward reaction, and the hemoglobin rose from 40 to 75 per cent. One week later, on retyping, the patient's blood cells were found to be Group A, Type N, Rh—, and his serum contained demonstrable anti-Rh agglutinins.

This boy with hemophilia required four transfusions because of serious blood loss from continued oozing from the gums. One week after the first transfusion and only four days after the last of a series, two more transfusions were given in succession, with evidence of an increasing hemolytic reaction at the end of the second transfusion. Blood typing at that time proved that the last donor used was Rh+, Group A, Type M. The patient appeared to be Group A, Type MN, and apparently Rh+, although under the microscope it was evident that most of the cells were unagglutinated. It was therefore presumed that some of the last donor's blood was still present in the recipient's circulation. The patient's serum failed to show any demonstrable agglutinin against the Rh factor. The following day two transfusions from Rh— donors were given with no untoward results. Nine days after the transfusion reaction, retyping of the patient's cells proved him to be Group A, Type N, Rh—. Therefore, the grouping carried out shortly after the transfusion reaction, which had identified the recipient's cells as belonging to Type MN, Rh+, was in fact performed with a mixture of the donor's Type M, Rh+ cells and the recipient's Type N, Rh— cells. After this last examination, the patient's serum demonstrated anti-Rh agglutinins. Antibodies against the Rh factor may develop in an Rh— recipient within a week, and these may subsequently cause a hemolytic transfusion reaction.

These experiences demonstrate that it is necessary to keep in mind that immediately after a relatively mild transfusion reaction the recipient's circulation may contain a mixture of donor's and recipient's blood cells, and that only careful examination of the results obtained by grouping and typing will disclose whether or not the patient is Rh+. Obviously such a reaction can only be found if the patient's serum contains a very weak agglutinin that fails to destroy all the infused cells.

Numerous cases of intragroup transfusion reaction with signs of hemolysis are now to be found

in the literature.<sup>23-38</sup> That the Rh factor is important and that Rh incompatibility between donor and recipient is the probable cause of most of these accidents have been amply proved. In our study of transfusion reactions in 32 patients in whom hemolysis was evident, it was found that errors in grouping were responsible in 3 cases, the presence of weak A<sub>2</sub> or A<sub>2</sub>B agglutinin in the donor's blood in 2, and Rh incompatibility in 27. Thus, it seems likely that 80 to 90 per cent of all hemolytic transfusion reactions can be explained on the basis of Rh incompatibility.<sup>39</sup>

In view of the widespread establishment of hospital and community blood banks during the last few years, particularly since the onset of the present war emergency, and the much more frequent use of the now readily available whole blood in the treatment of hemorrhage, shock and anemia, one may expect an increase in the incidence of hemolytic transfusion reactions, as a result chiefly of the sensitization of the Rh— persons who in previous transfusions had received Rh+ blood. This is of particular importance to the members of the armed forces, many of whom are given whole blood because of anemia and infection resulting from wounds. In contrast to the use of transfusion in civilian blood banks, where the majority of the patients are given only a single transfusion or a single series within a week or less, in the medical services of the armed forces the recipients often receive repeated transfusions. Hence, these Rh— recipients are much likelier to be immunized through the infusion of Rh+ red cells and, with each succeeding transfusion, to develop increasing signs of blood destruction, which may eventually cause damage to the kidneys. Although such patients do not necessarily develop fatal anuria, the unpleasantness of the post-transfusion reactions causes bitter complaint, and certainly the patient fails to benefit from the infused blood and the illness may be prolonged by anemia and excessive blood destruction.

It is therefore important that all transfusions be preceded by Rh typing of the recipient and, if an Rh— person is so identified, that only Rh— blood be used. This is particularly desirable when multiple transfusions are contemplated. Only under conditions of dire emergency should untyped blood be used or an untyped recipient be transfused. Even in such cases, blood banks in many of the large hospitals have available Rh— blood to give in transfusions when there is not sufficient time to carry out a complete grouping, typing and cross-matching.

An analysis of the transfusion reactions due to Rh incompatibility in 26 cases in which sensitization was due to previous transfusion shows that the reactions were mild (chills, fever and a decrease in hemoglobin level), in 5, moderately severe (pain

in the back, jaundice and slight hemoglobinuria) in 14 and severe (hemoglobinuria and anuria) in 7. No deaths occurred in this series.

(To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31161

#### PRESENTATION OF CASE

A seventy-year-old retired dentist entered the hospital complaining of a painful swollen right knee.

Three years before admission the patient came to the Out Patient Department because of a stiff and painful back. At that time he gave a vague story of having had pain and stiffness in the right knee for several years. He was definitely relieved after strapping. Twenty-eight months before entry he fell forward to the ground while gardening. Soon afterward he developed pain in the right loin, radiating to the right thigh and leg. He was most uncomfortable while lying in bed. When examined twenty-seven months before entry the lumbar spine was rigid but not tender. The right knee was limited in extension to 15° flexion. X-ray studies at that time showed marked lumbar lordosis and extensive spurring of the lumbar vertebrae, especially the third and fourth. There were marked osteophytes along the tibial joint surfaces of the right knee. Six months before admission he fell again, which caused stiffness and pain on motion in the right knee. He used a cane to get about. The pain and stiffness increased, and the joint became swollen. Two months before entry he began to use crutches. He had remained in bed for the past three weeks.

Physical examination revealed a thin, well-developed man. The right knee was limited in extension to 70° flexion, with approximately 15° of motion. It was swollen, brawny, warmer than the left knee and mottled red; it was tender and painful on motion. The heart was not remarkable, and the lungs were moderately emphysematous. A bifid coccyx was suspected.

The temperature, pulse and respirations were normal. The blood pressure was 170 systolic, 90 diastolic.

Examination of the blood revealed a white-cell count of 6000, with 68 per cent neutrophils, 22 per cent lymphocytes, 8 per cent monocytes and 2 per cent eosinophils. The urine was negative, the specific gravity being 1.012. The fasting blood sugar was 85 mg. per 100 cc., and the uric acid 4.1 mg.

X-ray films of the lumbar spine showed marked hypertrophic changes, with extensive spur forma-

tion and fusing of spurs between the third and fourth lumbar vertebrae, as well as irregularity of the adjoining surfaces of the bodies. The abdominal aorta showed marked arteriosclerosis. An x-ray film of the right knee showed a marked change compared with the examination two years previously. Considerable destruction of the femoral joint surface was seen. A small fracture line appeared to extend through one of the condyles anteriorly. The joint space was markedly narrowed, and there was considerable soft-tissue swelling, with probable fluid in the joint. All the bones of the joint showed marked decalcification extending well into the condyles. X-ray films of the heart and lungs were negative.

The right knee was put into suspension traction, and the joint was aspirated. Thick pus-like synovial fluid was withdrawn, which contained 34,500 white cells, with 92 per cent polymorphonuclears, 3 per cent lymphocytes and 5 per cent monocytes, and 29,000 red cells per cubic millimeter; there was mucin but no sugar. The cell count was probably inaccurate because the purulent material did not mix well in the counting fluid. A culture showed no growth. The sedimentation rate was 24 mm. in 60 minutes. A tuberculin test in a dilution of 1:100,000 was positive, presenting an 8-mm. area of redness and induration. The serum calcium was 8.8 mg. per 100 cc., the phosphorus 3.3 mg., and the phosphatase 3.1 Bodansky units.

In the forenoon of the fifth hospital day the patient had a sharp transient precordial pain, which radiated at once to the back and then disappeared. A few minutes later he again had severe pain, became markedly dyspneic and pulseless and expired.

#### DIFFERENTIAL DIAGNOSIS

DR. FRIEDRICH W. KLEMPERER: It is obvious that the terminal episode had no direct correlation to the chief complaint that brought the patient to the hospital. I shall try to discuss the joint disease first.

From the history we learn that the patient was suffering from chronic joint disease involving the spine and right knee. The total duration of the illness is not given accurately, but it certainly was greater than three years. The distribution of pain in the low back and loin and the radiation to the thigh are characteristic of involvement of the lumbar spine. It is the rule to see disappearance of back pain after complete fusion has developed. The involvement of the knee had progressed gradually over the course of years, with an acute exacerbation caused by injury six months before admission. This history of chronically progressive arthritis leads us to a differential diagnosis between chronic infection, such as tuberculosis, and rheumatoid arthritis.

Primary bone tumor seems less likely at this age. Metastatic malignancy might be considered, but of course the story is somewhat long and we have no evidence of a primary lesion. Pyogenic infection

\*On leave of absence.

also seems unlikely in view of the lack of acute symptoms as well as the duration. Could he have had a chronic osteomyelitis? I do not believe that this is likely, and the x-ray findings probably rule it out.

The physical findings are indicative of a chronic inflammatory lesion but do not rule out tumor. Again, an acute infectious process is ruled out by the absence of marked tenderness, redness and heat. The laboratory examinations are most helpful. First we hear that the aspirated knee fluid was pus-like and sterile. The fact that it was sterile is further evidence against pyogenic infection. A cell count of 34,500 may be seen in rheumatoid arthritis, although frank pus probably does not occur. Effusions due to tumor probably never show cell counts of this magnitude, and I am inclined to discard the diagnosis of tumor on that basis alone. The absence of sugar, frequently found in the presence of a high white-cell count, is often seen in tuberculosis. The elevated sedimentation rate is only a sign of active disease and not helpful in the differential diagnosis. A positive tuberculin test in a man of seventy is not diagnostic, but the violent reaction at a high dilution is in favor of the diagnosis of active tuberculosis. The phosphatase of 3.1 units serves to rule out such diseases as Paget's disease or tumor with osteoblastic activity. The x-ray films may be helpful.

DR. MILFORD D. SCHULZ: These films taken two years prior to the last admission merely show pronounced proliferative changes. The joint space is quite well preserved (Fig. 1). Two years later the joint space is practically gone, the medial surface of the tibia is partially destroyed, and the bones are quite decalcified (Fig. 2). Although the knee had been painful for two years the decalcification of the femur is not too bad. The spine looks just like that of an old man.

DR. KLEMPERER: Do you believe there is destruction in the area of the spine?

DR. SCHULZ: There is a large spur on the side of one vertebra, and I wonder how much of what we see is not this spur projected upon the vertebral body. In the anteroposterior view one cannot trace the vertebral surfaces.

DR. KLEMPERER: Are these areas of decreased density consistent with destruction?

DR. SCHULZ: They did not change in two years, which is curious if they were due to active destruction.

DR. KLEMPERER: It is obvious that at the time the first x-ray films were taken, two years ago, the patient presented the degenerative changes that a man of seventy is entitled to have, but I believe that there is also evidence of destruction in the spine. He had spurs completely bridging the anterior portions of the vertebrae and causing complete immobilization of the spine. If this was tuberculosis, the fusion due to degenerative changes would explain the lack of progression of the lesion, in analogy to what we see after artificial fusion as a therapeutic

measure. The diagnosis of a destructive lesion in the spine in addition to the apparent degenerative changes is also supported by the clinical symptoms. Severe pain is not usual in straight degenerative



FIGURE 1 Film of Knee Showing Proliferative Changes and Intact Joint Surface.

disease of the spine and always requires another explanation, which in this case would be tuberculosis. The rapid progression of destruction and decalcification of the knee are also not consistent with a diagnosis of rheumatoid arthritis. I have never seen a patient with rheumatoid arthritis who had developed such extensive destruction in only two years without showing involvement of many other joints. I believe that rheumatoid arthritis remains a possibility although not a likely one. The rapidity of progression, the degree of destruction and decalcification of the bones around the knee joint, the localization and the character of the joint fluid are certainly best explained by a chronic infectious process, which in all probability was tuberculosis.

In discussing the terminal episode one must remember that observations made during the last few minutes of the patient's life, frequently by unexperienced observers, are notoriously inaccurate. The only thing one can say with a fair degree of assurance is that this man died an acute circulatory death. The most probable assumption in a man of this age who has been put to bed and whose leg has been kept in suspension is that he had developed a phlebitis of the femoral veins that led to a massive pulmonary embolus. He may also have died from acute coronary thrombosis. I admit that both these diagnoses, particularly the first, are the likeliest

ones on a statistical basis. The history, however, fits another condition so well that I should like to hazard a probable diagnosis of dissecting aneurysm. The patient had been known to have hypertension, and according to the roentgenogram, the aorta was markedly calcified. These two conditions predispose to the formation of a dissecting aneurysm. The story of sudden sharp pain with radiation to the back is particularly characteristic of this condition. The second attack of pain may indicate that at that time the aneurysm had dissected upward and had perforated the pericardium and that the patient died

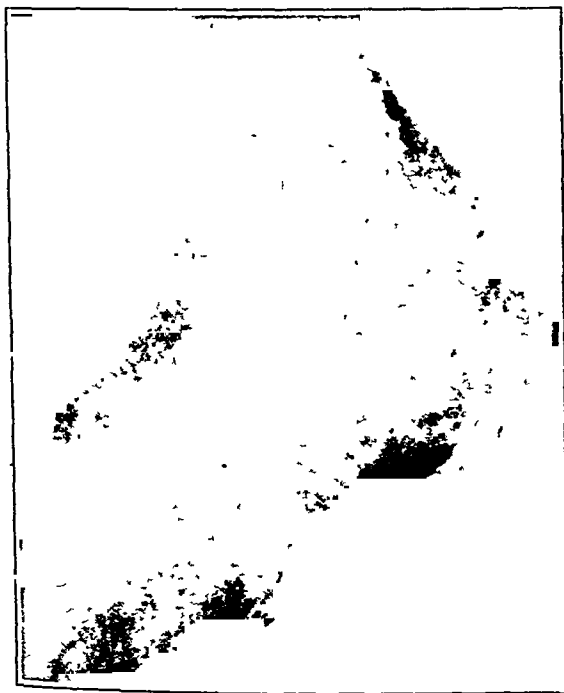


FIGURE 2 Film of Knee Two Years Later Showing Areas of Bone Destruction and Soft-Tissue Swelling.

of cardiac tamponade. I shall make this my first guess for the diagnosis of the final episode.

A PHYSICIAN: Does the fact that he had recurrent pain go against pulmonary embolism?

DR. KLEMPERER: I believe that that is against it.

#### CLINICAL DIAGNOSES

Suppurative arthritis, right knee.  
Coronary thrombosis.

#### DR. KLEMPERER'S DIAGNOSES

Tuberculosis involving lumbar spine and right knee  
Degenerative joint disease.  
Dissecting aneurysm of aorta?  
Pulmonary embolism?  
Coronary thrombosis?

#### ANATOMICAL DIAGNOSES

Tuberculosis of lumbar spine and right knee.  
Massive pulmonary embolus.

#### PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIFFEN: This man was killed by a massive pulmonary embolus. The fourth and fifth lumbar vertebrae contained many small nodules of soft white material, but they were not compressed. The right knee was swollen, and the joint cavity was filled with yellow pus. The synovia was redundant and rough, and the articular cartilages of the femur, tibia and patella were partially destroyed. Sections of the vertebrae and knee joint showed tuberculosis microscopically, and guinea pigs inoculated with material from the knee died of tuberculosis. The patient had no other signs of tuberculosis except for apical pulmonary adhesions.

#### CASE 31162

#### PRESENTATION OF CASE

*First admission.* A fifty-four-year-old shoe cutter was admitted to the hospital because of swelling of the abdomen.

One year prior to admission the patient developed a generalized itching unassociated with any skin lesion or jaundice. About two months later he noted increasing tiredness, although he was able to continue working. About six months before entry he noted swelling of the legs, brought on by standing for any length of time and disappearing after a night in bed. Soon thereafter he noticed that the abdomen was swollen and continued to enlarge, and a protrusion developed in the region of the umbilicus. Three months prior to entry he developed increasing dyspnea on exertion. A physician prescribed diuretic pills, following which the patient lost about 20 pounds in a few days. His abdomen, however, did not appreciably decrease in size. There was no history of gastric discomfort except for gaseous eructations after meals, and no hematemesis, melena or unusual stools. He had lost a "considerable" amount of weight over a period of six months.

The patient had been a rather heavy drinker of beer, augmented with whisky and rum, before the onset of his symptoms. There was no history of exposure to drugs and chemicals other than alcohol. He had had typhoid fever at the age of twenty. One and a half years before admission he had had a high-vein ligation in the right leg, and the veins of the left leg were injected at the same time.

Physical examination revealed a rather frail sallow man showing evidence of considerable weight loss. The lungs revealed fine moist rales at both bases, and diminished breath and voice sounds over



the entire chest. The diaphragm was high bilaterally. The heart sounds were clear, with splitting of both sounds and a questionable systolic murmur at the apex. The abdomen was markedly distended and tense, with shifting dullness and a fluid wave. A completely reducible umbilical hernia was present. No organs or masses were felt. A massive left scrotal hernia, completely reducible, was present. Both legs revealed evidences of stasis dermatitis. There was pitting edema of both feet, and induration of both legs to the knees. The knee and ankle jerks were not elicited, but other reflexes were normal.

The temperature was 98°F., the pulse 90, and the respirations 22. The blood pressure was 112 systolic, 70 diastolic.

Examination of the blood revealed a red-cell count of 4,300,000, with 12 gm. of hemoglobin, and a white-cell count of 7700, with 76 per cent neutrophils. The urine was negative. The serum non-protein nitrogen was 31 mg. per 100 cc., the protein 5.6 to 6.8 gm., with an albumin-globulin ratio of 1.05, and the chloride 95 milliequiv. per liter. A bromsulfalein test showed retention of 30 per cent of the dye. A cephalin flocculation test was  $\pm$  after twenty-four and forty-eight hours. Venous pressures taken in the antecubital space and femoral vein were equivalent to 18.5 and 14.5 cm. of water, respectively, on one occasion and to 20.5 cm. in both places on another. Fluid removed from the left chest had a specific gravity of 1.012, with a cell count of 1419 red cells and 138 white cells, of which 22 per cent were neutrophils, 76 per cent lymphocytes and 2 per cent eosinophils. Fluid from the abdominal cavity had a specific gravity of 1.014, with a cell count of 2610 red cells and 550 white cells, practically all of which were lymphocytes. The latter fluid contained 4.2 gm. of protein per 100 cc., and both the chest and ascitic fluids were negative for tubercle bacilli on smear and guinea-pig inoculation and for tumor cells. A sputum examination was negative for tubercle bacilli on smear. A blood Hinton test was negative.

A roentgenogram of the chest revealed a heart that was slightly enlarged but was within the limits of normal by measurement. There was a considerable amount of fluid in both pleural cavities. No liver shadow could be made out, and the hepatic flexure came almost to the diaphragm. The spleen was not enlarged. A barium swallow revealed a normal esophagus without evidence of obstruction or varices.

An electrocardiogram showed slight right-axis deviation. There were low-voltage QRS complexes and flat T waves in the standard leads.

The patient was placed on a high-calory, high-vitamin diet with fluids restricted to 2000 cc. daily. A peritoneoscopy was performed on the third hospital day. The right lobe of the liver presented a rounded edge that was just below the costal margin.

The left lobe presented a rounded edge that extended down to the level of the umbilicus. The surfaces of both lobes were extremely irregular and in places hobnailed, and they were covered almost everywhere with innumerable white pinpoint tubercles. Some of these tubercles were seen on the peritoneal surface of the abdominal wall, overlying the left lobe of the liver. The transverse colon, small bowel and omentum in the upper part of the abdomen were involved in a red inflammatory mass in which there were a few tubercles. The lower abdomen appeared essentially negative. A biopsy specimen from the anterior surface of the left lobe of the liver showed no obvious abnormality.

On the tenth hospital day a paradoxical pulse was noted, and two days later a pericardial friction rub was heard. A fluoroscopic examination of the chest at that time revealed a small cardiac beat and no localized enlargement. There was no evidence of pericardial calcification, but there seemed to be some evidence of pericardial adhesions about the heart. The circulation time (arm-to-tongue) was 30 seconds. In spite of these findings, the patient continued to improve. He gained 15 pounds without significant accumulation of ascitic fluid and was discharged to his home on the thirtieth hospital day.

*Second admission* (two months later). Following his discharge the patient felt well except for persistent exertional dyspnea and some increase in abdominal distention. He gained about 10 pounds. He was readmitted for re-evaluation of his condition with a possibility of operation.

Physical findings were essentially unchanged except that a pericardial friction rub was no longer heard. The heart sounds were muffled. The pulsus paradoxicus was still present. The neck veins were pulsating and distended, there was considerable ascites and edema of the legs and feet, and the superficial veins of the abdomen were prominent. A roentgenogram of the chest showed no definite change.

Several chest and abdominal taps were performed, and the patient was given injections of Mercupurin to relieve him of some of the fluid.

On the twenty-eighth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. CONGER WILLIAMS: The generalized itching without jaundice did not mean much to me in the light of what happened later, so I shall overlook it for the moment.

In the differential diagnosis of ascites, it is important to know whether or not there is leg edema and, if so, what the time relation of its onset is to that of the ascites. We are told here that swelling of the legs came on before the ascitic swelling was noticed. When the cause of ascites and leg edema is intra-abdominal, ascites develops first and

leg edema later, owing to pressure of fluid on the intra-abdominal veins. If, however, both are due to heart failure, edema of the legs commonly appears first. In the case of constrictive pericarditis, ascites is often out of proportion to the amount of leg edema and may appear first. In this case, the sequence of events is unusual for heart failure in that signs of peripheral congestion preceded dyspnea.

Obviously the diagnosis of cirrhosis of the liver was considered because of the history of alcoholism, but a search for esophageal varices was negative. The appearance of fluid in the legs before the development of ascites is also against the diagnosis. I suppose that the patient had varicose veins, but it does not say exactly why the vein was ligated. Obviously the injection was done for varicosities. Whether or not he had had thrombophlebitis, we do not know.

In brief, the cardiac findings on physical examination were not remarkable. Obviously the degree of ascites was out of proportion to the degree of leg edema.

We know nothing about the course of this man's temperature, either before or after admission.

In the differential diagnosis of edema, determination of the serum protein should be a routine procedure. The value of 5.6 to 6.8 gm. per 100 cc. is a little on the low side, but not low enough to be significant.

Thirty per cent dye retention in the bromsulfalein test is a moderately abnormal finding, but it is found in cases of simple liver congestion, without much in the way of parenchymal liver disease. Also, the cephalin flocculation test was equivocal, and can be explained on a basis of liver congestion alone.

The venous pressure readings were abnormally high, a finding of greater importance in making the differential diagnosis than any other reported physical or laboratory finding. I shall discuss it later in greater detail.

The characteristics of the abdominal fluid suggest an exudate rather than a transudate. The protein was high, the specific gravity was fairly high, and the cell count suggests more of a lymphocytosis than one expects from an ordinary bloody tap. So it is likely that a factor other than increased venous pressure was active in the production of ascites. The question of infection with tubercle bacilli is one of the most important things to consider in the differential diagnosis of ascites. A negative finding, however, especially on examination of the sediment of the ascitic fluid, means nothing. I think one can say that in tuberculous peritonitis one seldom gets a positive smear for acid-fast bacilli. Furthermore, it has been said that guinea-pig inoculations are positive in only about 50 per cent of cases. Thus, the negative findings in both these determinations mean little. Also, the fact that the sputum was negative for tubercle bacilli is of little consequence.

DR. LAURENCE L. ROBBINS: I have not been able to find the films taken on the first admission. I gather, however, that there was no change in the appearance of the heart or lungs. Someone made the statement that the heart was within normal limits of size by measurement. In none of these films is it possible to see the cardiac shadow sufficiently to be certain of it. This observation must have been made by the fluoroscopist. The fact that there was a small beat is of some importance.

DR. WILLIAMS: How about a large amount of pericardial fluid? Is that possible with this sort of right border?

DR. ROBBINS: It depends on how much you mean by a "large amount." There can be a lot of fluid in the pericardial cavity even with that configuration.

The lung fields are not remarkable. So far as I can see there is no evidence of disease in the lower and upper lobes, other than this linear fibrosis in the apices, which indicates a previous infection.

DR. WILLIAMS: Is this shadow the septum of the middle lobe?

DR. ROBBINS: Yes; with some fluid extending into it.

DR. WILLIAMS: These pictures are not particularly helpful, but I did not expect them to be. We know that he had fluid in the chest, because of the findings on physical examination and because of the fact that a goodly amount was withdrawn.

I saw the electrocardiograms, and the low voltage and the flat T waves are suggestive of pericardial involvement, which fits in later in the differential diagnosis.

I wonder whether the apparent hobnailed surface of the liver was related to the tubercles on the peritoneal surface. The record states that the biopsy showed no apparent intrahepatic disease. I do not believe that that means much one way or another. It is definitely stated, however, that tubercles were seen on the edge of the liver. The question I should like to raise is, Were these real tubercles or something simulating them? It is well known that widespread carcinoma may mimic tuberculosis, in the gross at any rate. We have no report of a histologic examination. I think it most probable, however, that these were real. The description of the transverse colon sounds like localized tuberculous infection in the abdomen.

A paradoxical pulse was noted. The question here is whether it actually appeared at that time or whether it was noted for the first time, having been present previously. It seems unlikely that a paradoxical pulse would develop so fast, unless there was a considerable amount of pericardial effusion. The x-ray picture suggests that the effusion, if any, was insignificant. Since there apparently was no great change in the blood pressure, and no sudden change in the clinical state, I am doubtful about the presence of pericardial tamponade. I suspect that pericardial involvement had been present for some time before the onset of symptoms, and that

the paradoxical pulse was also present long before it was observed for the first time. The friction rub suggests that there was acute inflammation of some part of the pericardium. Of course that often takes place in the presence of old pericardial fibrous changes. The small amplitude of heart beat may have been due to old pericardial adhesions. The absence of pericardial calcification means nothing in deciding on the presence of constrictive pericarditis.

It is quite likely that dyspnea at the time of the second admission, as well as on previous occasions, was due to an accumulation of fluid in the chest. Also, dyspnea is a symptom of constrictive pericarditis.

In describing a paradoxical pulse, the variation in systolic blood pressure between inspiration and expiration should be recorded. A good many normal people have a paradoxical pulse of slight degree, and it is often quite marked in bronchial asthma. The use of the term, "pulsus paradoxicus" without qualification is not especially helpful. In this case, however, the finding is significant, especially in association with distended and pulsating neck veins. The latter observation was not recorded until the second admission, but the high venous-pressure measurement suggests that visible venous pulsations in the upright position were also present at the time of the first admission.

I wonder whether the operation mentioned was an abdominal or thoracic procedure. Abdominal exploration is sometimes performed in tuberculous peritonitis. I suspect, however, that this was a thoracic operation and that it probably consisted of a pericardial exploration, because everything in the history points to a diagnosis of constrictive pericarditis — a high venous pressure in association with ascites, leg edema and the finding of a paradoxical pulse. Also the electrocardiographic findings are typical, and the absence of normal pulsation on fluoroscopic examination is suggestive. Also significant is the apparent absence of intracardiac involvement to explain the high venous pressure. I am therefore practically forced to accept the diagnosis of constrictive pericarditis.

The next question is, What is the relation of this to an apparent tuberculous peritonitis? Was the constrictive pericarditis also tuberculous, or was it the much more frequent nonspecific pericarditis, complicated by tuberculous peritonitis? It is more logical to suspect that the picture can be explained on the basis of a long-standing tuberculous constrictive pericarditis in association with tuberculosis of other serous surfaces, including the pleura and peritoneum. Tuberculous peritonitis alone does not explain the increased venous pressure and the findings in the lungs, unless one assumes that there was an independent tuberculous pleural process going on. We therefore must assume that something was going on outside the abdomen. One might say that

the absence of fever and the increased white-cell count are perhaps against the diagnosis of tuberculous peritonitis, but we do not have a detailed record of the temperature. It is possible to have this picture caused by tuberculosis and at the same time to have a normal temperature. It is not usual, however, to have a high white-cell count in association with tuberculous peritonitis.

If this is tuberculosis, and it seems likely that it is, the next question that comes up is, Where was the original focus? So far as I can tell it was not in the lungs; perhaps it was in the mediastinum or elsewhere. It is true that cases like this usually have an obvious primary tuberculous focus. All I can say is that it just was not found.

#### CLINICAL DIAGNOSES

Polyserositis, with chronic constrictive pericarditis.  
Bronchopneumonia.

#### DR. WILLIAMS'S DIAGNOSES

Tuberculous constrictive pericarditis.  
Tuberculous peritonitis.

#### ANATOMICAL DIAGNOSIS

Polyserositis.

#### PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIFFEN: I am sorry that Dr. White is not here, since he followed this patient rather closely through his medical career. Neither is Dr. Sweet, who performed the operation. Before he operated, Dr. Sweet made the remark that this type of case was most unfavorable for pericardiectomy, as judged from the experience of this clinic and others, because of the obvious activity of the process. But in view of the patient's continued downhill course he did operate and found a constrictive pericarditis. Thereupon he removed strips of the thickened pericardium from the anterior surface. After operation the patient did extremely well for a few months. It was seven months before he came in again, at which time he was in much the same condition as before operation. It is a little unusual for a patient to do so well postoperatively and then fail rapidly within a few months. Generally speaking, if the operation is not helpful there is no postoperative interval of improvement.

At the time of death the patient showed peripheral edema of the lower extremities to the knees. He had prominent neck and chest veins. In the distended abdomen there were umbilical and left inguinal hernias. The abdominal cavity was striking in that all the peritoneal surfaces were greatly thickened and appeared milky. This process involved the liver and spleen, and had produced adhesions around these organs. The serosa of the gastrointestinal tract was tremendously thickened,

but there were no adhesions between the various loops of bowel. The liver weighed 1980 gm. and, on section, showed a distinct lobular architecture and was quite tough. Microscopically the liver showed advanced central congestion and necrosis leading to an early cardiac cirrhosis. Each pleural cavity was largely obliterated by fibrous adhesions and contained about 100 cc. of fluid. There were also adhesions between the medial surfaces of the lungs and the pericardium. The entire pericardium was tremendously thickened, and the heart was fixed to the anterior chest wall and to the posterior mediastinal structures. The thickening was most impressive over the auricles, especially the right,

where it measured as much as 1 cm. The orifice of the superior vena cava was narrowed to slightly more than 1 cm. in diameter. The orifice of the inferior vena cava, however, was capacious, measuring 3 cm. in diameter. The hepatic veins entering the inferior vena cava were not appreciably narrowed. The heart itself was not enlarged and revealed no intrinsic disease.

A blood culture and cultures of the fluid from the various cavities were negative, and guinea-pig inoculations were negative. Sections from the various serous surfaces showed a nonspecific subacute inflammatory process, with the laying down of many layers of collagen.

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## CANCER

AGAIN, April, by proclamation of President Roosevelt, is Cancer Control Month. During total war one might expect interest in cancer to assume a lesser place in one's thoughts than in times of peace; on the contrary, interest in it has rapidly increased. Perhaps the fact that cancer maims in an indiscriminate way on the home front and has killed more Americans since 1941 than has the war explains this phenomenon. The problem that cancer poses is formidable but by no means insoluble. As most members of the medical profession know, valuable new knowledge concerning cancer is being discovered daily and each bit of added knowledge

solves or leads to the solution of some small part of the total problem.

For a long time the earnest workers studying cancer have been discouraged by the magnitude of the problem and the narrowness of the fronts on which it has been faced. In spite of generous gifts supporting cancer research, the total amount available is completely inadequate to make sufficiently broad studies.

Until recently, the efforts of the American Cancer Society have been in the fields of lay and medical education and in aiding the care of impoverished patients. This year for the first time, as previously mentioned in the March 22 issue of the *Journal*, the society is tackling the problem of supporting studies of cancer, in addition to increasing its unremitting efforts to spread present knowledge. A statement appearing elsewhere in this issue of the *Journal* describes this new departure in the society's affairs and its organization to an attempt to raise \$5,000,000.

## THE RH BLOOD FACTOR

THE modern physician believes that mystery in medicine is as outmoded as is black magic. He is no longer afraid to tell his patients that he does not know a few of the secrets of the human body, and with him the aura of infallibility of a former generation is as obsolete as are its plug hats, its chin whiskers and its calomel measured on a knife blade. Medicine, today, is willing and eager to share its knowledge with its public. It asks only that all the facts be made known, that the case be temperately stated and that the hopes and the fears of human kind be not exploited in the interests of sensational journalism.

Too often, however, the newspapers and the magazines are a jump ahead of us and are peddling their borrowed wares on a bull market before most of us who should be best informed are ourselves thoroughly acquainted with the facts of the case. It is because of the half informed and poorly informed opinion that is already attaching itself to the mysteries of the Rh blood factor that the *Journal*

is presenting on other pages herein a thorough exposition of this recent addition to medical knowledge.

As recently as 1940, Landsteiner and Wiener, studying the agglutinins developed in certain experimental animals against the red blood cells of the rhesus monkey, found that approximately 85 per cent of human bloods contained an antigenic substance that was capable of reacting with this antibody. The agglutininogen was named the Rh factor, and bloods possessing it were called Rh+. Bloods lacking the factor were called Rh-. Persons with Rh- blood may become sensitized to the Rh factor by means of transfusions of Rh+ blood or, in the case of women, by bearing an Rh+ infant, the result of mating with an Rh+ man.

The practical importance of the Rh factor concerns Rh- women and their Rh+ offsprings, since, as has been stated, an Rh- person may become sensitized to Rh+ cells by an Rh+ transfusion, rendering subsequent Rh+ transfusions dangerous. Initial pregnancies with Rh+ infants may similarly sensitize the mother, producing in her blood agglutinins that will destroy the red cells of subsequent Rh+ infants, thus causing the anemia known as erythroblastosis fetalis; even the first infant of a mother who has been previously sensitized by one or more Rh+ transfusions may similarly suffer.

The inferences are obvious. Rh- persons should not receive repeated transfusions from Rh+ donors; Rh- women of child-bearing age should be protected completely against Rh+ transfusions because of the possible dangers to subsequent infants; and Rh- women mated to Rh+ men should, if one or more Rh+ children have been borne, be watched through subsequent pregnancies in order that proper measures may be taken to protect the infants.

An important point to remember is that the Rh factor, recently discovered although present for untold generations, is no cause for panic. In only about one fifteenth of the cases in which an Rh- woman is married to an Rh+ man is the infant likely to develop erythroblastosis unless Rh+ transfusions have been previously given to the mother, and less than one sixth of the infants so affected who recover suffer serious consequences in later life. As the author points out:

Since the placental barrier is assumed to hold back cellular elements, since some persons do not respond to Rh antigen by anti-Rh production, since 49 per cent of Rh+ men are heterozygous and can father Rh- children and since two or more pregnancies are usually necessary to produce infants suffering from erythroblastosis fetalis, this disease remains a fairly rare complication of Rh differences between mates. It may even be suggested that other incompatibilities between man and wife are more hazardous to married life than differences in the Rh factor.

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON CANCER

The following statement signed by the Massachusetts members of the American Cancer Society is endorsed by the Committee on Cancer and recommended to the members of the Massachusetts Medical Society for careful study and action.

G. A. MOORE, *Chairman*

\* \* \*

By the time this appears in print the medical profession and the public will have heard over the radio and seen in print many statements concerning the campaign of the American Cancer Society to raise \$5,000,000 for cancer research and other aid to cancer patients. This society was formerly known as the American Society for the Control of Cancer. It was founded some forty years ago and has shown a steady, sound growth in activities and strength during this time. It has been particularly active in the fields of lay and professional education. During the last eight years its growth has been aided by the large number of members of its Field Army. This subsidiary organization has given devoted service in promoting cancer education and in providing financial and other aid to impecunious cancer patients. It is active in every state except Massachusetts, where the Department of Public Health carries on these activities in an efficient manner.

Although several foundations spend sums of money for the support of cancer research, the money available for organized research each year amounts to less than \$1,500,000 for the country as a whole. On the other hand, cancer is killing over 160,000 people annually, and causing an expense and loss totaling many hundred millions of dollars. The officers of the American Cancer Society have long believed that this was not nearly enough support for a sufficiently broad study of this complicated disease and have secured the aid of far-sighted laymen in an effort to broaden the financial base supporting research on cancer and the care of patients with cancer. This lay committee is headed by Mr. Eric A. Johnston, president of the United States Chamber of Commerce, and the Executive Council is made up of distinguished men all over the country. Included are Mr. Robert Choate, publisher, *Boston Herald*, Mr. William K. Jackson, vice-president, United Fruit Company, and Mr. Sinclair Weeks, former United States senator and chairman of the Board of Directors, Reed and Barton. This committee ensures that the money-raising campaign will be well carried out.

Plans for spending the money raised provide for an equitable division of funds, with slightly more than 50 per cent to be allocated to the subsidiary state organizations, subject to approval of the parent society, and the remainder to the American Cancer Society. The bulk of the funds expended by the latter will go to cancer research in all its aspects, and some of the locally administered funds will also go to research. In addition, care of patients, facilities for treatment and many other cancer activities will be aided by increased support. That these activities will be efficiently carried out is indicated by the character of the officers, who are as follows: chairman of Board of Directors, Herman C. Pitts, M.D., consultant, Department of Cancer Research, Rhode Island Hospital, Providence; president, Frank E. Adair, M.D.,

chairman, Cancer Commission, American College of Surgeons, and surgeon-in-chief, Memorial Hospital, New York City; vice-president, Edwin P. Lehman, M.D., chief surgeon, University of Virginia Hospital and professor of surgery, University of Virginia Medical School, Charlottesville, Virginia; and treasurer, James J. Ripley, M.D.; and secretary, Eugene P. Pendergrass, M.D., director of radiology, University of Pennsylvania Hospital, Philadelphia. The Executive Committee is composed of these officers and the following: James B. Murphy, M.D., director of cancer research, Rockefeller Institute, New York City; Colonel C. P. Rhoads,

## MISCELLANY

### "A SPOT ON THE LUNG"

Joseph Conrad once said, "A word carries far — very far — deals destruction through time as the bullets go flying through space." Medicine has a few such words. Too often these are used when a serious or potentially serious condition must be explained to an apprehensive patient. When words treacherously lull either the patient or the physician into a false sense of security, then words may ultimately maim or destroy as

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To co-operate with the American Cancer Society, we, the physician members of the society who live in Massachusetts are forming a subsidiary organization. A layman's campaign committee has been appointed, with Mr. Arthur T. Lyman, of Westwood, as chairman, Mr. Ralph Lowell, of Westwood, as treasurer, Mr. Herbert T. Hand, Jr., of Boston, as director of publicity, Mr. George A. Baker, of Milton, as vice-chairman in charge of Greater Boston, and Mrs. William Brace Pratt, of Milton, as chairman of the Women's Division.

The American Cancer Society will welcome any aid that physicians can give to the success of this campaign. Doctors can well afford to give themselves and should urge their patients to give. Send a check today; do not wait for a solicitor to ask you for money because this year's campaign is so organized that personal solicitation cannot be made. Remember that you, in spite of being a physician, have as much chance of dying of cancer as any of your patients. This chance is one in eight for men, and one in five for women. Your money now may save your life later. An office has been opened at 186 Tremont Street, Boston, the telephone number being LIBerty 0240. Checks made out to the American Cancer Society may be sent to the above address or merely mailed to "Cancer," care of your local postmaster.

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Nobody who has searchingly studied the histories of patients with pulmonary disease can doubt that the real function of the phrase, "a spot on the lung," is to cloud the facts. It is a cloak for a great variety of pulmonary diseases, a protective screen for the inability or unwillingness of the physician to arrive at a diagnosis acceptable to himself, a disguise for a bitter truth that the physician hesitates to tell the patient, an escape for the patient who tries to elude further diagnostic work and necessary treatment. After all, one does not die of "a spot on the lung," but one can die of bronchial carcinoma and one might die of pulmonary tuberculosis. Along with much other evasive, medical double-talk, "a spot on the lung" is a verbal mechanism of escape from reality. In the same category belongs the term "a touch of tuberculosis" and, improperly applied, "nothing but a little thickened pleura."

No physician needs to be told that "a spot on the lung" is no diagnosis. He realizes that it is evidence, on the one hand, of healed disease which calls neither for treatment nor for alarming its bearer, or, on the other, of active disease in need of treatment. The physician sometimes uses the term in patients in whom he has failed to establish, with a certainty that carries conviction for himself, the difference between an active disease and obsolete scar. "A spot on the lung" has a pleasantly innocent sound. It lulls into inertia and indifference whatever doubts or curiosity the patient and, even in some cases, the doctor may have. But still it is, for the physician, a mental reservation. It seems to beckon as a safe place to stand if "a spot on the lung" later turns out to be carcinoma, tuberculosis or bronchiectasis.

Admittedly, this judgment may be harsh. But I dare say that it will be resented only by those who, with the instrumentality of this ambiguous term, neglect their obligation of persevering until "a spot on the lung" has been accurately diagnosed. No person need be told that he has "a spot on the lung." If the condition is as clinically insignificant as the term suggests, the patient should be told that he has a scar from a previous tuberculous infection — one that needs an occasional checkup or one that needs no further observation. Or when the diagnosis is certain, the patient should be told that his lungs are normal. For, while "a spot on the

lung" is often the obscured beginnings of destructive disease, it is, in other cases, the starting point for tuberculo-phobia and anxiety neuroses, conditions that are no less crippling and hardly more easily curable than tuberculosis itself.

But, though every reflecting physician knows that "a spot on the lung" is a meaningless and dangerous term, the utter convenience of the expression — and others like it — militates against their prompt extinction. Past experience justifies a pessimistic outlook. No amount and intensity of medical education are likely to eliminate entirely the term from medical parlance. Medical education, however, is being overtaken by the information that the public, including the prospective patient, is acquiring. People are learning to realize fully the confusing ambiguity of the term, they are beginning to refuse its acceptance just as an enlightened consumer protests against ambiguous and misleading labels on packaged goods. And the comparison is eminently proper: for all intents and purposes, "a spot on the lung" is ambiguous and misleading labeling. It may well be that through the protest of the consumer, by the refusal of every layman to be satisfied with the pseudo-diagnosis of "a spot on the lung" the term will eventually disappear.

It is high time for the medical and nursing professions and everyone engaged in tuberculosis work to bury a medical term that has quite literally buried so many patients. — Reprinted from *Tuberculosis Abstracts*, April, 1945.

## CORRESPONDENCE

### PENICILLIN THERAPY OF NEUROSYPHILIS

*To the Editor:* Following the use of penicillin for the treatment of early syphilis, there has been wide interest in its use in neurosyphilis. A study of this problem has been in progress at the Boston Psychopathic Hospital for over a year. Under the direction of the Department of Therapeutic Research of this hospital, working under contract with the Committee on Medical Research of the Office of Scientific Research and Development, Drs. Harry C. Solomon, Augustus S. Rose and Laurence D. Trevett have been treating cases of asymptomatic neurosyphilis, general paresis, tabes dorsalis, meningo-vascular syphilis, syphilitic optic atrophy and syphilitic meningitis. In some cases, malaria or fever-cabinet (diathermy) therapy has also been employed.

Physicians and clinics having such cases under their care are invited to send them to the Out-Patient Clinic at 74 Fenwood Road on Tuesday or Saturday morning from 8:30 to 10:00. A consultation will be held at that time, and arrangements will be made for the admission and treatment of suitable cases. There is no charge for the penicillin, and the ward rates for the patients are reduced in case of need. There are suitable wards for asymptomatic and other nonpsychotic cases. In each case, the welfare of the patient is the primary consideration.

HARRY C. SOLOMON, M.D., *Director*  
Boston Psychopathic Hospital

74 Fenwood Road  
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### CAUSE OF DEATH IN DIABETES

*To the Editor:* Everyone will welcome the article "The Cause of Death in Diabetes," by Drs. S. L. Robbins and A. W. Tucker, which appeared in the December 28, 1944, issue of the *Journal*. First of all, it again permits hope for those with diabetes, because the authors state that significant changes in the pancreas were observed in only 36 per cent of the 184 patients in whom the condition of the pancreas was noted. Von Noorden never saw nor have I ever seen a patient who was 100 per cent diabetic. Although the authors found significant changes in only 36 per cent of their cases, they did note some degree of change in the pancreas in an additional 6.5 per cent, which brings the total percentage of pancreatic lesions up to 42.5 per cent, as compared with the 74 per cent noted by Dr. Shields Warren.<sup>1</sup>

What enables one to make a diagnosis of diabetes post mortem must remain for pathologists to decide, but to me it hardly seems proper that this should be based solely on "glycogen nephrosis" or so-called 'Armanni-Ebstein cells' in the tubular epithelium of the loops of Henle," because the authors frankly state that, with the passing years, the finding of glycogen nephrosis has become increasingly less frequent, suggesting that adequate therapy may prevent this

type of secondary lesion. In contrast to the labile character of glycogen nephrosis, I should like to point out that hyalinization or fibrosis of the islands of Langerhans after it has once occurred does not disappear. Their criterion is of interest because of the recent article by Laipply, Eitzen and Dutra<sup>2</sup> on intercapillary glomerulosclerosis in which an incidence of 63.7 per cent of this type of lesion in diabetic autopsies is recorded and is used as their diagnostic criterion of diabetes. Robbins and Tucker, on the other hand, found intercapillary glomerulosclerosis, all degrees combined, in only 20 per cent of their cases. Such a seeming divergence of views is confusing to a clinician. I suspect that, if slides from 100 autopsies on diabetic patients were prepared and submitted to Drs. Robbins and Tucker, to Drs Laipply, Eitzen and Dutra and to Dr. Shields Warren, there would be far less difference of opinion than now appears to exist. It might also be advantageous in this connection to have an additional report on the diagnostic value of lesions of the kidneys in alloxan diabetes.

Coma as a cause of death occurred in a surprisingly small number of cases, there being but 22 in the 307 analyzed. Good as these figures are, I believe that, if the staff physicians of the Boston City Hospital now reviewed the treatment of these 22 cases, they would be able to state that, if these patients were to re-enter the hospital, the number of deaths could be materially reduced, possibly by as much as a half. That would be a worth-while study, and I hope that my suggestion will be considered constructive. Incidentally, it would be of interest to know the average age at death of the 22 patients with diabetic coma.

The authors draw comparisons between causes of death in the diabetic and nondiabetic groups, as recorded in their Table 1. There are similarities and differences that are of interest. Thus, vascular disease caused 35.2 per cent of the deaths in the diabetic group, and 27.1 per cent in the nondiabetic cases. It is interesting to compare the figures for these two groups with that for our group of 929 clinical cases.<sup>3</sup> Obviously, a sizable difference in any one item in one group will, other things being equal, force a consistent disparity in the others. Doctors Robbins and Tucker recognize this difficulty and call attention to it when they state that they threw the coma cases out of consideration. Furthermore, they explain the disparity in the percentages of coronary deaths in their two series and in the generally accepted clinical figure by the statements that their definition of coronary occlusion as a cause of death is quite precise and that "a certain percentage of acute coronary deaths are handled by the Medical Examiner's Office and hence are not available for inclusion within this series." In our clinical series, vascular disease was listed as the cause of death in 60 per cent of the cases.

Pulmonary infections in the diabetic series amounted to 25.6 per cent, and in the nondiabetic group to 24.2 per cent, as compared with 11.3 per cent in our clinical series.

Cancer was the cause of death in only 8.4 per cent of the diabetic group, as compared with 14.7 per cent in the nondiabetic group. This agrees with the 8.2 per cent in our clinical series, but the latter, however, is overweighted because of the influence of the numerous cancer cases in the Palmer Division of the New England Deaconess Hospital, which are included in our series. It is not at all surprising that the diabetic group at the Boston City Hospital showed a lower cancer death rate than did the nondiabetic group. It is true that the ages at death were the same, but the length of exposure to cancer of the diabetic patient is limited to the period that involves the duration of his diabetes and is quite different from that of the nondiabetic patient. In order to make accurate comparisons of this nature, what is needed, of course, is material by which one can compute death rates for the representative groups. If the higher mortality of the diabetic patient, as compared with the nondiabetic, were taken into account, many differences, on a percentage basis, would be wiped out; at the same time, those conditions to which the diabetic patient was prone would be thrown into even sharper relief. It might well be found, for example, that the cancer death rate was little different among diabetic and nondiabetic patients. All this indicates that, although this usual type of analysis is useful, one must keep in mind that the interpretation of such analyses should recognize its limitations. Furthermore, there is the fundamental consideration that there may be an association between the two diseases. This is discussed in detail by Wilson and Maher.<sup>4</sup>



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## THE TREATMENT OF BACTERIAL ENDOCARDITIS WITH PENICILLIN

### Experiences at the Boston City Hospital During 1944\*

MANSON MEADS, M.D.,† H. WILLIAM HARRIS, M.D.,‡ AND MAXWELL FINLAND, M.D.§

WITH THE TECHNICAL ASSISTANCE OF CLARE WILCOX

BOSTON

FLEMING,<sup>1</sup> in his original studies on the antibacterial action of cultures of his strain of *Penicillium*, included some strains of *Streptococcus viridans*, which he found to vary considerably in their susceptibility. Others<sup>2-3</sup> have since confirmed these findings with more purified preparations of penicillin in vitro, noting the wide differences in susceptibility of single strains and finding some to be relatively resistant. Clinical trials in the treatment of subacute bacterial endocarditis were begun in 1942. The earliest reports were somewhat discouraging,<sup>9-16</sup> but they did suggest the possibility that larger doses of penicillin given over a longer time might produce better results. Although negative blood cultures were usually obtained for brief periods during the administration of the small doses, bacteremia recurred after the treatment was ended.<sup>9, 11, 12, 14</sup>

Loewe and his associates,<sup>17</sup> early in 1944, reported favorable results in 7 consecutive cases of subacute bacterial endocarditis with combined heparin and penicillin treatment, but their cases had been followed for only a short time when this report was made. Later in the year, as larger amounts of penicillin became available, additional encouraging reports began to appear.<sup>18, 19</sup>

In this paper are presented the findings in 9 cases of subacute bacterial endocarditis caused by *Str. viridans* and in 7 proved or probable cases of acute bacterial endocarditis due to other organisms, all of which were treated with sodium penicillin at the Boston City Hospital during 1944. The final evaluation of the results in surviving cases must, of course, depend on observations of a larger number of cases followed for a considerably longer period. The purpose of this presentation is to bring out some of the problems encountered during the treatment and in the immediately ensuing period. For convenience the cases will be considered according to their bacterial etiology, but the features are shown together for all the cases in the accompanying tables, and the relevant findings in single cases appear in the text figures.

CASES OF SUBACUTE BACTERIAL ENDOCARDITIS

*Patients and methods.* The 9 patients included in this study represent consecutive, unselected but typical cases of subacute bacterial endocarditis admitted to the medical wards of the Boston City Hospital between February and October, 1944. The diagnosis was based on the finding of multiple positive blood cultures, embolic manifestations and evidence of valvular heart disease. The patients ranged in age between nineteen and fifty-seven years; 5 were under thirty and 4 were over forty. Five were females and 4 were males. All had received courses of one or more of the sulfonamides without benefit before penicillin was started, but sulfonamides were not used during the penicillin treatment. They were sometimes given later for special indications.

Penicillin treatment was begun only after multiple positive blood cultures had been obtained. It was usually given by repeated intramuscular injections and only occasionally by constant intravenous infusion in either 0.85 per cent sodium chloride or 5 per cent glucose solution in water, using a total of 1500 to 2000 cc. per day. A predetermined dosage was used to start the treatment, usually 25,000 units every two hours intramuscularly, but this was altered later according to the clinical response or the serum concentrations obtained.

\*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

Presented, in part, at a meeting of the New England Heart Association, Boston, November 20, 1944.

Most of the penicillin used in this study was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

†Research fellow in medicine, Harvard Medical School and Thorndike Memorial Laboratory.

‡Research fellow, Thorndike Memorial Laboratory.

§Assistant professor of medicine, Harvard Medical School; chief, Fourth Medical Service, and associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

Acute pyelonephritis as a cause of death was far higher in the diabetic series (7.3 per cent) than in the nondiabetic series (1.6 per cent). The incidence was only 1.7 per cent in our clinical series, but I am sure that the autopsied series is more accurate in this respect. With increasing apprehension we behold such cases after observing uncontrolled diabetes of about fifteen years' duration in young people, and I am positive that the danger of its occurrence should be emphasized. One would like to know the sex of the patients. At one time we thought there was a predominance of females, but we have no analysis of recent data. I have recently discussed disease of the kidneys in uncontrolled diabetes.

The incidences of tuberculosis were about the same in both autopsied groups, being 5.6 per cent for the diabetic series and 8.0 per cent for the nondiabetic. In our clinical series, tuberculosis was recorded as a cause of death in 3.6 per cent of the cases.

In their conclusions the authors state, "The diabetic patient lives as long as the nondiabetic." I wonder if they would wish to modify this sentence or in some way to reconcile their statement on longevity of the diabetic as compared to the nondiabetic patient. The former do not live so long as the latter. In our latest compilation, the average duration of the disease was 13.7 years, although 18.2 per cent of the patients lived over twenty years. In fact, the life expectancy of our diabetic patients is about two thirds as long as that of nondiabetic patients. The authors seem to have overlooked the facts that the usual figures for the expectation of life relate to the expectation at birth and that in referring to the expectation of life for diabetic patients one should take account of the age at which the diagnosis of diabetes was first made. Thus, Table 45 on page 279 of our book<sup>1</sup> shows the expectation of life for the general population and for diabetic patients according to different age groups. It was prepared with the co-operation of the Statistical Bureau of the Metropolitan Life Insurance Company and is based on death rates of each age subsequent to first observation, regardless of the duration of the diabetes. The table is as follows:

Expectation of Life for the General Population and for Diabetic Patients.

AGE	NORMAL WHITE PERSONS	DIABETIC PATIENTS
10	57	40
20	48	33
30	39	28
40	31	21
50	23	14
60	16	10
65	12	8

From the above table it will be seen that the expectancy of life for the diabetic patient is approximately two thirds that of the general population for each age group.

Among the valuable hints that the article contains is the statement, "The example of a cerebral hemorrhage found at autopsy as a cause of death in a case clinically diagnosed as a diabetic coma is a not infrequent occurrence." Speaking for the group of doctors at the New England Deaconess Hospital, we can confirm that statement. In fact, we are beginning to have almost as many cases sent into the hospital with an erroneous diagnosis of diabetic coma as there are cases of diabetic coma itself. We welcome such cases, because the patients are generally very seriously ill and therefore just the ones to be separated promptly from coma cases by proper laboratory tests. A blood carbon-dioxide combining power of 20 vol. per cent or lower is a good differential standard and serves as the greatest common divisor among the symptoms and signs of diabetic coma. That one sentence in the article will, I believe, do a great deal of good, because it emphasizes the necessity for all hospitals to provide laboratory service for diabetic emergencies.

ELLIOTT P. JOSLIN, M.D.

81 Bay State Road  
Boston

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2. Laipply, T. C., Eitzen, O., and Dutra, F. R. Inter-capillary glomerulo-sclerosis. *Arch. Int. Med.* 74:354-364, 1944.

3. Joslin, E. P., Root, H. F., White, P., and Marble, A. *Treatment of Diabetes Mellitus*. Seventh edition. 707 pp. Philadelphia: Lea & Febiger, 1941.  
4. Wilson, E. B., and Mather, H. C. Cancer and tuberculosis, with some comments on cancer and other diseases. *Am. J. Cancer* 16:227-250, 1932.  
5. Joslin, E. P. Management of diabetes mellitus in general practice. *M. Clin. North America* 28:1054-1066, 1944.

Dr. Joslin's letter was referred to Dr. Robbins for comment. His reply is as follows:

To the Editor: Dr. Tucker and I greatly appreciate Dr. Elliott Joslin's interest in our article. The point that the life expectancy of diabetic patients is only two thirds as long as that of nondiabetic patients is extremely valuable and well taken.

Two questions that were raised can be answered. The average age at death in the coma group of patients was 46.7 years. In agreement with Dr. Joslin's impression, females outnumbered males by a ratio of 2:1 in our series of patients dying of acute pyelonephritis. The total number of cases involved, however, appeared to be too small to warrant any conclusion regarding sex predominance in this disease.

S. L. ROBBINS, M.D.

Mallory Institute of Pathology  
Boston City Hospital  
Boston

NEED FOR PHYSICIANS IN VETERANS ADMINISTRATION

To the Editor: I desire to bring to your attention the need of physicians for Rating Board work in the Boston office of the Veterans Administration.

A rating board is an agency of the Veterans Administration composed of a medical member, a claims member (attorney) and an occupational member, who pass on claims for benefits administered by the Administration and evaluate the degree of disability resulting from disease or injury. The medical member of this board reviews physical examinations and medical records from various sources and advises the board on all questions of medicine and resulting disability. The work is sedentary in nature and is quiet and dignified in character.

The hours of employment are forty-eight hours per week. The basic salary is \$3800 which, with the overtime now in effect, totals \$4424 per year, less the necessary deductions for retirement and tax purposes. The work may be considered reasonably permanent in nature, and this office is interested in receiving inquiries from physicians meeting the requirements of Civil Service, which are essential to employment in a federal agency.

It would be appreciated if this need were brought to the attention of your readers, as I am certain, that with the present numerous vacancies for physicians in the Veterans Administration there is work for all who are qualified or interested in this type of employment, particularly that type of man who, with a good medical background, cannot, because of some physical impairment, engage in active general practice.

A. A. DOUCET, Assistant Manager

Veterans Administration  
Post Office Building  
Boston 9

NOTICES

ANNOUNCEMENT

Dr. Jonathan Zonis announces the removal of his office from 300 Seaver Street, Roxbury, to the Asthma and Hay Fever Clinic, 10616 Euclid Avenue, Cleveland, Ohio.

BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the Mallory Amphitheater, Pathology Building, Boston City Hospital, on Wednesday, April 25, at 12 m. Dr. Frank H. Lahey will discuss "Lesions of the Stomach, Duodenum and Jejunum."

(Notices continued on page xix)

after three weeks in Case 7, and after seven weeks in Case 8. Recurrences occurred in Cases 6 and 7; these will be considered separately.

**Sensitivity of the organisms.** Data concerning the organisms obtained from the blood cultures are shown in Table 2. The strains of *Str. viridans*

ologic response to smaller doses, or because the clinical response was inadequate, or when the serum concentration could not be maintained above the M. I. C. for the patient's strain. Attempts were made to achieve the desired effect in some of the patients by giving hourly intramuscular doses, in

TABLE 2 Results of Blood Cultures

CASE No	No OF CULTURES POSITIVE BEFORE PENICILLIN	ORGANISM	M I C (PENICILLIN SENSITIVITY*)	TIME AFTER BEGINNING OF THERAPY	
				LAST POSITIVE	FIRST NEGATIVE
1	3	<i>Str viridans</i>	0.016	16 hr	18 hr
2	4	<i>Str viridans</i>	0.022	0	4½
3	5	<i>Str viridans</i>	0.031	72	120
4	8	<i>Str viridans</i>	0.031	21	30
5	4	<i>Str viridans</i>	0.031	48	72
6	6	<i>Str viridans</i>	0.031	6	8
7 (a)	9	<i>Str viridans</i>	0.031	2	4
(b)	1	<i>Str viridans</i>	0.008	48 (before)†	0
8	17	<i>Str viridans</i>	0.011	24	48
9	0	<i>Str viridans</i>	0.022	Post-mortem	—
10	9	Type 7, pneumococcus	0.011	0	4
11	3	Type 5, pneumococcus	0.011	0	3½
12	6	Type 6, pneumococcus	0.011	4	8
13	6	<i>Str haemolyticus</i> (Group A, Type 2b)	0.008	0	24
14	1	<i>Str haemolyticus</i> (Group A)	0.008	Post-mortem	—
15	4	Gonococcus	—	48 (before)‡	48 (before)
16	1	<i>Staph aureus</i>	0.01	24	120

\*Units of penicillin added to 1 cc of culture (containing 1000 to 10,000 organisms) that gives no growth in 24 hours

†The only positive culture during the relapse was obtained 48 hours before the second course of penicillin was started

‡Blood cultures became negative after treatment with sulfamerazine and 48 hours before penicillin was begun

varied in their sensitivity to penicillin, the M. I. C. (minimum inhibiting concentration) ranging from 0.011 to 0.031 Oxford units per cubic centimeter of

others by constant intravenous infusions and, in some patients who were in congestive failure, by reducing the fluid intake. The actual amounts of penicillin given are shown in Table 3. Treatment was continued for twelve to nineteen days except in Case 9, in which death occurred on the seventh

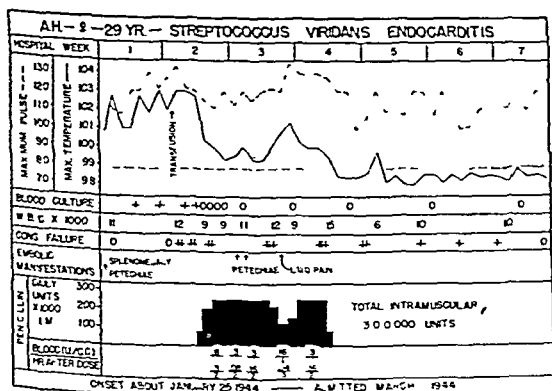


FIGURE 2. Case 2.

Shortly before penicillin therapy was started the patient developed congestive failure, which increased during the course of the treatment. She subsequently regained compensation and no longer requires digitalis. Adequate blood concentrations were maintained with small doses in this case.

culture containing 1000 to 10,000 streptococci. Some of the organisms were tested several times with results varying twofold in either direction on different occasions.

**Penicillin dosage.** The dose most often used was 25,000 units intramuscularly every two hours. Variations from this dosage were made either for the purpose of observing the clinical and bacteri-

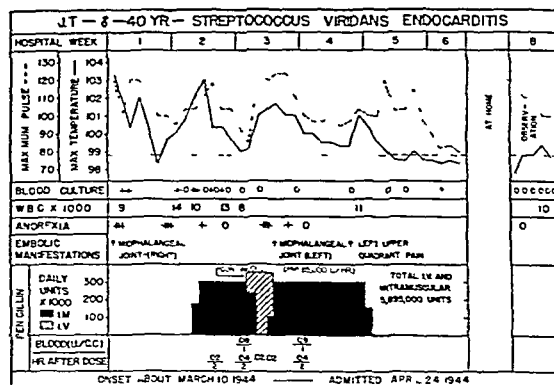


FIGURE 3. Case 3.

Because bacteriostatic levels were not regularly maintained for two hours after 25,000 units intramuscularly the patient was given penicillin by constant intravenous drip at the rate of 15,000 units per hour for three days. During this time there was a return of fever and the intramuscular method was resumed. The patient was readmitted for further observations because of contaminants grown in the last blood culture obtained before discharge. No evidence of a recurrence of infection was found.

day after almost 2,000,000 units had been given. The total amount used in the remaining cases varied

The organisms varied in their rate of growth in blood cultures and in subcultures. They were characteristic strains of *Str. viridans* that failed to react with serums of the Lancefield Groups A, B, C, D and G.\* The organisms were tested for their sensitivity to penicillin by the method of Rammelkamp and Maxon,<sup>20</sup> modified in later tests only by the use of 0.5-cc. amounts of broth for making the penicillin dilutions. The concentrations of penicillin in the serum were determined by the serial dilution method of Rammelkamp.<sup>21</sup> From three to seventeen positive blood cultures, with an average of seven, were obtained in each case before penicillin treatment was begun.

Blood cultures were also taken at frequent intervals early in the course of the penicillin treatment and then twice weekly until discharge. Further blood cultures were taken during follow-up examinations. In the latter part of the study, penicillinase† was added to the culture medium when blood was obtained for culture during penicillin therapy.

Heparin was given to 3 of the patients by continuous intravenous infusion. The amount was adjusted in an attempt to keep the blood clotting time at about 60 minutes (range, 30 to 120 minutes).‡ This usually required about 200 to 250 mg. daily. Heparin was discontinued when hemorrhages or other untoward reactions occurred.

Some of the highlights of the clinical course, the treatment and the laboratory findings in the individual cases are shown in Figures 1 to 9.

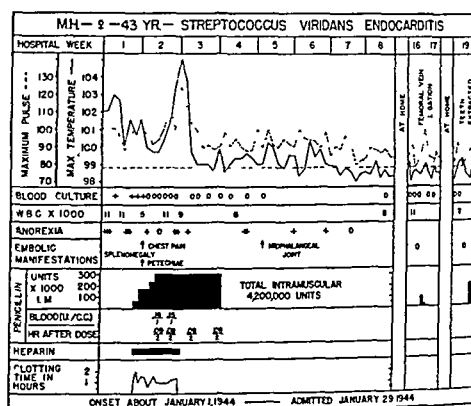


FIGURE 1. Case 1.

The patient began to improve soon after treatment with heparin and penicillin was started. The marked rise in temperature after a week of treatment was accompanied by malaise, anorexia, nausea and abdominal discomfort. Fever and symptoms subsided within a few hours after heparin was stopped. During each of two subsequent admissions she had a short course of penicillin; the first was given before and after femoral-vein ligations for thrombophlebitis, and the second was given before and after extraction of infected teeth.

*Duration before treatment.* Some of the relevant dates in each of the cases are listed in Table 1. The

TABLE 1. Significant Dates.

CASE No.	AGE	SEX	DATE OF HOSPITAL ENTRY	DATE OF FIRST SYMPTOM	DATE PENICILLIN BEGUN	DATE WHEN AFEBRILE	DATE LAST SEEN
1	37	F	Jan. 29	Jan. 1	Feb. 4	Feb. 13	Dec. 15
2	29	F	Mar. 1	Jan. 25	Mar. 11	Mar. 13	Nov. 15
3	40	M	Apr. 24	Mar. 10	May 3	May 13	Nov. 15
4	20	F	May 27	May 20	June 5	June 19	Nov. 15
5	19	F	July 20	July 1	July 25	July 26	Nov. 15
6†	25	M	Oct. 17	May 1*	Oct. 25	Oct. 26	Dec. 1
7‡ (a)	57	M	Apr. 17	Feb. 9	May 8	May 10	Dec. 15
(b)			Oct. 27	Sept. 25	Oct. 30	Nov. 4	May 17 (died)
8§	49	M	Dec. 16*	Oct. 15*	Feb. 4	Feb. 14	May 25
9	21	F	May 8	Apr. 25	May 16	Died	
10	35	M	Feb. 6	Jan. 28	Feb. 21	Mar. 4	Nov. 22
11	65	M	Jan. 19	Jan. 17	Mar. 14	Mar. 15	Nov. 15
12	55	M	Jan. 30	Jan. 24	Feb. 4	Died	Feb. 11
13	34	F	Apr. 8	Mar. 25	Apr. 15	Apr. 19	Nov. 25
14	73	M	Apr. 14	Not known	Apr. 21	Died	Apr. 21
15	20	F	Apr. 15	Mar. 25	Apr. 28	Died	May 1
16	52	M	Oct. 28	Oct. 26	Oct. 28	Died	Nov. 13

\*1943 (all others 1944).

†Patient readmitted for a recurrence.

‡Two admissions, indicated as (a) and (b).

§Patient died during a readmission for cardiac failure.

The patients were examined daily during treatment and at frequent intervals thereafter for evidence of embolic phenomena, changes in cardiac murmurs and other complications.

\*We are indebted to Miss Ruth M. Drew of the Department of Bacteriology and Immunology, Harvard Medical School, for the streptococcus groupings and typings.

†Supplied by Drs. H. J. White and R. O. Roblin, Jr., of the Stamford Laboratories, American Cyanamid Company.

‡The heparin administration and blood studies in these cases were carried out by Drs. C. S. Davidson and John H. Freed.

time of onset of symptoms as given by the patient is necessarily only approximate, and there is reason to believe that the disease was active in most cases for a longer period. The duration of symptoms of active infection at the time of admission to the hospital was five weeks or less in 6 of the cases, about two months in 2 cases and almost one and a half years in Case 6. Treatment with penicillin was started within ten days after entry of 7 of the cases,

wise varied. In each of the recovered cases, however, these findings were normal before the patient left the hospital. The hemoglobin and red-cell counts likewise returned to normal except in Case 6, which will be referred to later.

Enlargement of the spleen was noted before treatment was begun in 4 cases (Cases 1, 2, 5 and 6), and

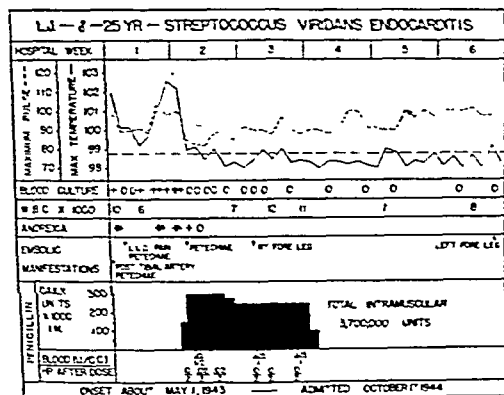


FIGURE 6. Case 6.

The patient had symptoms of active infection for about one and a half years before admission to the hospital. He improved rapidly after penicillin was started, although adequate blood levels were not maintained in his blood. Before discharge he had evidence of embolism to the leg, and four weeks later he had a recurrence of symptoms of active infection and a positive blood culture. He was readmitted and again improved on penicillin but more slowly than previously.

there was tenderness over the spleen in 2 of them. The spleen remained palpable throughout most of

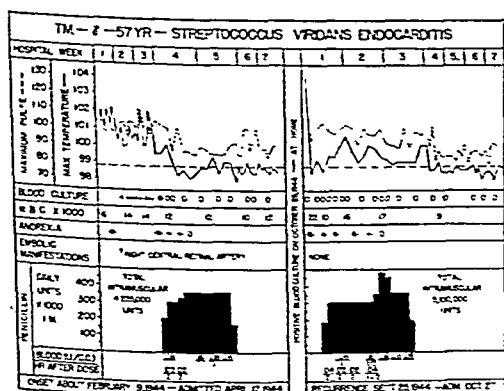


FIGURE 7. Case 7.

In this case it was not possible to maintain adequate levels with 25,000 units every two hours and the dosage was changed to 15,000 units every hour. There was a recurrence of symptoms, and a single positive blood culture was obtained after four and a half months. A second course of penicillin was then given in spite of the fact that other blood cultures were negative. The patient again showed a good clinical response to the treatment.

the course of treatment in these 4 cases, but receded later and was no longer palpable at the time of the last examination in any of the living patients. In no case was enlargement of the spleen seen for the first time after the treatment was started.

*Effect on bacteremia.* Data indicating the effect of penicillin treatment on the results of blood cultures are shown in Table 2. The numbers of positive cultures obtained in each case before treatment was

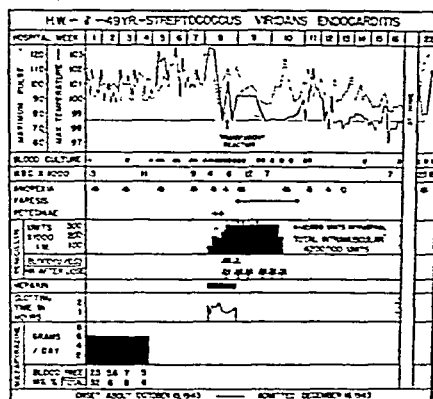


FIGURE 8. Case 8.

Adequate levels were readily maintained in this case, and the patient improved soon after treatment with heparin and penicillin was started. On the fifth day of treatment the patient became comatose and developed hemiparesis. The cerebrospinal fluid was bloody and showed organisms on smear that could not be cultured. Heparin was discontinued, and three intraspinal injections of penicillin were given. The patient recovered from this episode and improved steadily but continued to have poor cardiac function. He died three and a half months later in what seemed to be so-called "forward failure." At autopsy there was healing of the remnants of vegetations on the aortic valve; occasional organisms were seen in the smears of the ground-up vegetations, but cultures yielded no growth. There was a large splenic abscess, from which *Streptococcus viridans* was grown.

begun are also listed. The last positive culture was obtained before the first dose in Case 2 and from two to seventy-two hours after treatment was begun in the remaining cases except Case 9, in which the cardiac blood obtained at autopsy was positive in

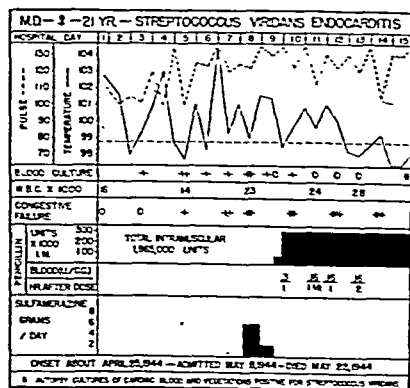


FIGURE 9. Case 9.

The patient had had symptoms for only three weeks and had developed severe congestive failure before treatment with penicillin was started. Although high blood concentrations were readily maintained, the patient died after seven days of the treatment, and *Streptococcus viridans* was grown from the cardiac blood and vegetations.

spite of more than six days of treatment. Subsequent blood cultures in the living cases were all

from 3,000,000 to 6,000,000 units except in Cases 6 and 7, in both of which a total of more than 9,000,000 units was given in two separate courses.

**Heparin.** This drug was used in Cases 1, 4 and 8. In Cases 1 and 4 it was discontinued after eight and twelve days; respectively, because of the occurrence of a rising temperature and pulse rate associated

TABLE 3. Summary of Therapy.

CASE NO.	SIZE OF DOSE	INTERVAL	PENICILLIN THERAPY* NO. OF DOSES	TOTAL DOSAGE	DURATION	DURATION OF HEPARIN THERAPY
	units $\times 10^3$	hr.		units $\times 10^3$	days	days
1	15	2	35	4200	16	8
	25	2	147			
2	15	2	10	3010	14	—
	20	2	88			
	15	3	16			
	20	2	43			
3	25	2	76	5895	19	—
	360	2	127			
4	15	2	30	5550	19	12
	10	1	58			
	15	1	177			
	25	2	84			
	25	2	35	3555	13	—
	20	2	134			
6	25	2	60	3700	14	—
	20	2	110			
7(a)	25	2	37	4225	12½	—
	15	1	220			
(b)	25	2	112	5100	15	—
	20	1	46			
	15	1	92			
8	15	2	35	4200	16	5
	25	2	147			
9	25	2	74	1865	6	—
10	15	2	219	3285	18	21
11	15	2	48	975	6	—
12	15	2	36	1840	7	7
	25	2	52			
13	100	3	77	1455	14	—
	15	3	2	30	¾	—
14	15	3	22	330	3	—
15	15	2	5	3820	16	—
	15	3	21			
	20	2	172			

## Notes:

Case 2. Levels on 3-hourly dosage adequate during congestive failure.

Case 3. Levels were inadequate during intravenous therapy and symptoms recurred.

Case 4. Patient given 20,000 units every 2 hours for 3 days after a splenic infarct, which occurred 16 days after the main course of penicillin.

Case 5. Patient weighed 90 lb.; blood levels were adequate on lower doses.

Case 6. Best clinical response; bacteriostatic levels only for 1 hour after injection.

Case 7. Recurrence (positive blood culture and chills) after 5½ months.

Case 8. Penicillin given intrathecally for 3 days because of pleocytosis and organisms seen (cultures negative) in spinal fluid during hemiparesis.

Case 11. Intrathecal doses for 6 days for meningitis.

Case 12. Intrathecal doses last 4 days for meningitis.

Case 16. Intrathecal doses during first 10 days for meningitis.

\*All injections were given intramuscularly in the order noted, with two exceptions, the second series in Case 3 and the first in Case 13 (in each, the figure is the daily intravenous dose, which was continued for 3 days).

with malaise, sweating, anorexia, nausea, drowsiness and irritability. All these symptoms completely subsided within twelve hours after the heparin was stopped. It was therefore assumed that these findings represented an untoward reaction or sensitization to heparin similar to drug fever or serum sickness. In Case 8, the heparin administration was stopped on the fifth day, after the sudden occurrence of hemiparesis associated with grossly bloody cerebrospinal fluid.

*Effect of penicillin on the symptoms and signs of infection.* The clinical course in those who did not have serious complications was marked by an increase in appetite, a decrease in irritability and sweat-

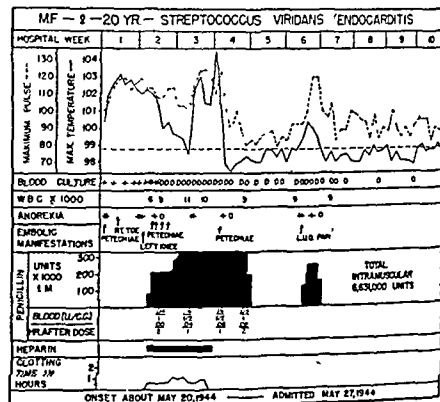


FIGURE 4. Case 4.

In this case, small doses of penicillin were used during the first five days but they were later increased. The marked rise in temperature lasting about four days was accompanied by vague discomforts, all of which subsided, together with the fever, promptly after the heparin was discontinued. A second course of penicillin was given for three days following the occurrence of a splenic infarct and fever eleven days after the first course was completed.

ing and a general feeling of well-being, which began twenty-four to forty-eight hours after the penicillin was started. In 4 of the cases, the fever subsided, with the oral temperature dropping and remaining below 100°F., within forty-eight hours, whereas in the other 4, excluding Case 9, some fever continued during nine to fourteen days of treatment (Table 1). There was an occasional rise in temperature later in some of the cases, either associated with embolic manifestations or arising from causes not related to the major illness.

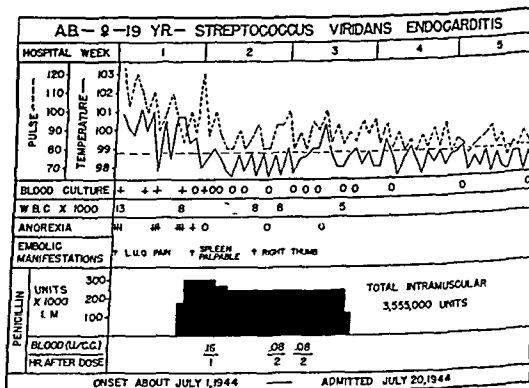


FIGURE 5. Case 5.

The patient weighed only about 90 pounds, and high levels were maintained on doses of 20,000 units every two hours.

The white-cell counts were only slightly elevated in most cases, and the effect of treatment was variable. The erythrocyte sedimentation rates like-

*Recurrences or possible reinfections.* Thus far there has been a recurrence of symptoms and of bacteremia in 2 cases. Case 7 was one in which, because of the failure to maintain bacteriostatic levels throughout the two-hour period after an intramuscular dose of 25,000 units, the patient was given 15,000 units every hour; he seemed to improve following this change. Four months after the treatment was stopped the patient had a recurrence of the original symptoms, and a single positive blood culture was obtained four weeks later. Other blood cultures both before and after this positive one were negative. The patient was nevertheless given another course of penicillin, with rapid alleviation of the symptoms. Interestingly enough, the organism obtained during the recurrence grew more

*Complications.* There were no untoward reactions to the penicillin except for the temporary local discomfort of the injections. Besides the embolic manifestations the only significant complication was the occurrence of thrombophlebitis of the legs in 2 patients. Interestingly enough, one of these patients received heparin through an arm vein, and in both cases the penicillin was given entirely by intramuscular injection. In Case 1, swelling and pain in one leg began before the patient left the hospital. She was readmitted and had a bilateral femoral ligation because of increasing edema and discomfort, and was given a few doses of penicillin before and after the operation. She was subsequently readmitted for extraction of teeth and was again given penicillin before and for twenty-four hours after

TABLE 5. *Cardiac Findings.*

CASE No.	HISTORY OF RHEUMATIC INFECTION*	VALVES INVOLVED CLINICALLY	CARDIAC STATUS		
			BEFORE THERAPY Grade	DURING PENICILLIN Grade	AT LAST OBSERVATION Grade
1	+	Mitral and aortic	II	II	II
2	+	Mitral	IV	IV	I
3	0 (23)*	Mitral	II	II	II
4	+	Mitral and aortic	I	I	I
5	+	Mitral	I	I	I
6	+	Mitral and aortic	II	II	II
7 (a)	0 (14)*	Mitral	II	II	
(b)		Mitral	II	II	II
8	0 (6)*	Mitral and aortic	III	III	Dead
9	+	Mitral and aortic	IV	IV	Dead
10	+	Mitral	I	I	I
11	0	None	I	I	I
12	0	Aortic	IV	IV	Dead
13	0	Aortic	III	IV	I
14	?	None	I	I	Dead
15	0	Aortic	I	IV	Dead
16	0	None	I	IV	Dead

\*In 3 cases with no history of rheumatic infection, the figures represent the number of years that the patient had been aware of having a cardiac murmur.

slowly, had a somewhat different colony morphology and, in parallel tests, was more sensitive to penicillin than the one obtained originally (Table 2). No peripheral embolic manifestations were seen during this recurrence.

Another patient (Case 6) was recently readmitted. One week after his discharge from the hospital, he developed a cold with coryza and headache and a few days later again had chills, fever and sweats. New crops of petechiae appeared on the trunk, and there were several tender nodular lesions on the fingers and toes. Several positive blood cultures were obtained, but in this case the organisms had about the same sensitivity to penicillin as those obtained originally, although they too grew somewhat more slowly and in smaller colonies. The symptomatic response to the second course of penicillin was not nearly so striking as that to the initial course. The patient became bacteria-free after fifteen hours and improved symptomatically after three days of treatment.

this procedure. The other patient (Case 7) developed pain and tenderness in the popliteal region with a rise in fever before the completion of the second course of penicillin. This all cleared without special treatment. In Case 6, there was a thrombophlebitis at the site of the constant intravenous infusion during the second course of treatment.

*Fatal cases.* Two of the 9 patients died, one (Case 9) after only six days of treatment and the other (Case 8) three months after the treatment was completed (Table 6). The former had marked congestive failure, which remained unaffected by treatment with penicillin and digitalis. In this case it was possible to maintain high levels, well above the M. I. C. for the patient's own strain, throughout the two-hour interval between doses. Blood cultures taken after the second day of penicillin were negative, but a culture of the cardiac blood at autopsy was positive, and the organisms were seen in smears and grown in cultures of the large vegetation that was found on the aortic valve.



negative except during the recurrences in Cases 6 and 7. In 3 of the cases the blood cultures were negative in four to eight hours and in a fourth case within 18 hours after the initial dose of penicillin. The heart blood obtained at autopsy in Case 8 was sterile in spite of the fact that no penicillin had been given for the preceding three months.

**Embolic manifestations.** Signs and symptoms interpreted as evidence of embolic phenomena of one form or another were noted in each of the nine patients with *Str. viridans* endocarditis before treatment with penicillin was begun (Table 4). In most

TABLE 4. Occurrence of Embolic Manifestations in Relation to Penicillin Therapy.

CASE No	BEFORE THERAPY	DURING THERAPY	AFTER THERAPY
1	+	+*†	+
2	+	+	0
3	+	+	0
4	+	+*†	+
5	+	+	0
6	+	+	+
7 (a)	+	0	0
(b)	0	0	0
8	+	+*	0
9	+	0	—
10	+	0	0
11	+	0	0
12	+	+*	—
13	0	0	0
14	+	0	—
15	+	0	—
16	+	0	—

\*Embolic manifestations occurred during treatment with heparin.

†Positive blood culture obtained at the time when the embolic manifestations were observed (in the remaining cases, all blood cultures taken when emboli occurred during or after penicillin treatment showed no growth)

‡Embolic phenomena occurred after heparin had been discontinued

of the cases there were multiple manifestations. Lesions of the extremities, including the joints, were noted in 7 cases, splenic infarction in 4, hematuria in 3, crops of petechiae in 3, occlusion of the central retinal artery in 1, and a pulmonary infarct in 1.

In each of the 3 patients who were treated with heparin, similar occurrences were noted during its administration. In Case 1, crops of petechiae appeared for the first time and chest pain occurred on the day after the heparin was started. A blood culture taken at the time was positive. In Case 4, several crops of petechiae were noted during the heparin administration, and again after it was discontinued but while the penicillin was still being given. In this case many blood cultures taken when these petechiae were noted all showed no growth. In Case 8, a few petechiae were noted for the first time during the heparin treatment, and on the fifth day of this therapy the patient became comatose and developed a hemiparesis. A lumbar puncture done at that time yielded cerebrospinal fluid that was grossly bloody and showed typical short chains of gram-positive cocci in the smear, but culture of the fluid gave no growth. Penicillin was nevertheless given intrathecally in 10,000-unit doses after each of three lumbar punctures.

At first it was thought that these phenomena were associated with the heparin administration, but similar ones occurred in 4 other patients during treatment with penicillin alone. Crops of petechiae were noted during the penicillin therapy in Cases 2 and 6, splenic infarcts, with pain and tenderness in the left upper quadrant, in Cases 2, 3 and 5 and lesions of the joints and extremities in Cases 3, 4 and 6. All the blood cultures taken when these occurred were negative.

In 3 of the cases, lesions occurred in seven to fourteen days after the completion of the penicillin therapy. These involved a finger joint in Case 1, the left foreleg in Case 6 and the spleen in Case 4. In these cases also, all the blood cultures taken at the time were negative. Slight fever, anorexia and malaise were associated with these manifestations. The splenic infarct in Case 4 occurred after a large splenic abscess was discovered at autopsy in Case 8, and for this reason the patient was given a course of penicillin for three days—20,000 units every two hours.

**Cardiac findings.** A history of previous rheumatic fever was obtained in 6 cases (Table 5). The other 3 patients were aware of having cardiac murmurs for six to twenty-three years, although they had had no previous rheumatic manifestations. Clinically, the mitral valve alone was considered to be involved in 4 cases and both the mitral and aortic valves in the other 5. In 2 of the former, there was no evidence of stenosis, that is, only a systolic murmur was heard, — whereas in 1 of the latter (Case 8), only the aortic valve was found to be involved at autopsy.

Two of the patients were apparently well compensated throughout the period of observation. The other 7 had some degree of failure, which was classified, according to *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*,<sup>22</sup> as Grade II in 4 cases, Grade III in 1 case, and Grade IV in 2 cases. One of the patients (Case 8) had been taking digitalis for a long time, and in 2 other cases it had been given for only two days before penicillin treatment was begun. In Cases 2 and 9, congestive failure was increasing progressively just prior to the penicillin therapy, and in the former case this was apparently precipitated by a blood transfusion.

In this group of cases of *Str. viridans* endocarditis the development of congestive failure during or soon after the course of penicillin did not occur. Failure was aggravated in some cases, but the cardiac status remained essentially unchanged in most cases. In Case 2, there was decided improvement during convalescence, and the patient since leaving the hospital has been able to carry on considerable activity without dyspnea or edema. One patient (Case 8) who had marked aortic insufficiency died three months after the penicillin treatment with marked failure but without any evidence of pulmonary or peripheral congestion.

enlargement of the spleen. He was treated with heparin intravenously and with 15,000 units of penicillin intramuscularly every two hours. Blood cultures taken four hours after the first dose and

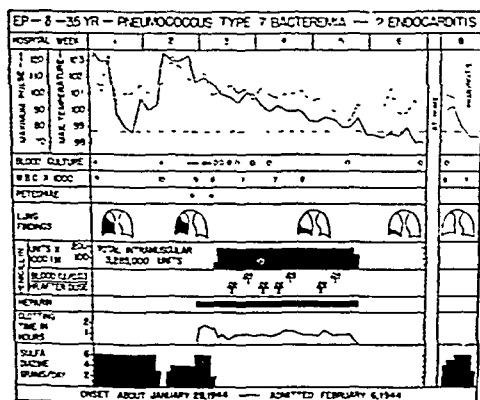


FIGURE 10. Case 10.

This patient had rheumatic heart disease with mitral insufficiency but was well compensated. Following typical lobar pneumonia he had a persistent bacteremia in spite of sulfadiazine therapy and then developed enlargement of the spleen. A few petechiae appeared before and soon after treatment with heparin and penicillin was started, but he improved rapidly thereafter. He was readmitted and treated with sulfadiazine for an attack of pharyngitis and has been well since then.

many taken later showed no growth. The lungs cleared rapidly. The spleen has receded and is no longer palpable, the heart has remained fully compensated, and the patient has remained well and able to carry on his usual work.

The second patient (Case 11, Fig. 11) had Type 5 pneumococcus pneumonia with bacteremia. This

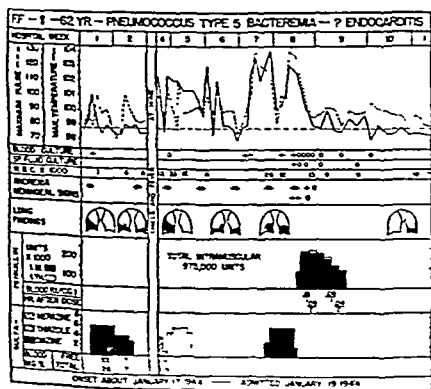


FIGURE 11. Case 11.

The patient was originally admitted to the hospital for lobar pneumonia with bacteremia, which apparently responded favorably to sulfonamide therapy. Soon after discharge he had chills and fever and was readmitted. Signs of pneumonia were still present, and the patient did not improve with further sulfonamide therapy. Bacteremia then recurred and persisted in spite of chemotherapy, and he developed purulent pneumococcal meningitis. Treatment with penicillin was followed by complete clinical and bacteriologic recovery.

apparently responded to treatment with sulfadiazine, and he was discharged after two weeks.

He returned ten days later with fever, sweats, leukocytosis and persistent signs in the lungs and was again treated with sulfonamides. Bacteremia nevertheless recurred, and the patient developed purulent meningitis with Type 5 pneumococci in the spinal fluid while still on full doses of sulfadiazine. He was then given 15,000 units of penicillin intramuscularly every two hours for six days and also intrathecal injections of 10,000 units after each lumbar puncture. The bacteremia and meningitis cleared rapidly, and the patient has remained well. In this case there were no signs or symptoms pointing directly to cardiac involvement.

In Case 12 (Fig. 12), there was a persistent Type 6 pneumococcus bacteremia without any known focus or antecedent infection. The patient denied any history of rheumatic infections but had an aortic stenosis and regurgitation and was in cardiac failure. Treatment with heparin intravenously and penicillin intramuscularly was begun on what was apparently the eleventh day after the onset of

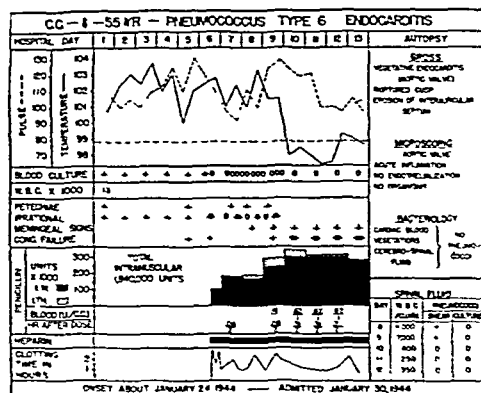


FIGURE 12. Case 12.

In this case there was persistent bacteremia with aortic endocarditis and no other demonstrable focus of infection when treatment with penicillin and heparin was started. The patient became comatose, and purulent meningitis was found on the third day of treatment; the latter improved with intrathecal penicillin. Congestive failure was present before treatment, but this increased suddenly and changes in the cardiac murmurs were heard shortly before death.

symptoms. The patient was given 15,000 units of penicillin every two hours for three days and then 25,000 units every two hours. Blood cultures taken eight hours after the first dose and several times thereafter showed no growth. On the fourth day of treatment the patient developed signs of meningitis. A lumbar puncture yielded cloudy fluid with a polymorphonuclear pleocytosis and with gram-positive diplococci in moderate numbers in the smears. Cultures of the first and subsequent cerebrospinal fluid specimens yielded no growth. Penicillin was given intrathecally after each of the lumbar punctures, which were done at twelve to eighteen-hour intervals. On the seventh day, after he seemed to be improving, the patient suddenly developed extreme dyspnea, followed by Cheyne-

In Case 8, infection was apparently controlled, but the patient did not regain compensation and continued to be weak and drowsy. He died a few days after re-entry to the hospital. A markedly hypertrophied and dilated heart was found at autopsy with small healing stumps of vegetations on the aortic valve. Smears of these vegetations showed rare organisms, but cultures were negative. There was a large abscess in the spleen, and a culture of pus from it yielded *Str. viridans*. The sensitivity of this strain to penicillin was the same as of that originally obtained from the blood.

One additional fatal case should be briefly mentioned. In this case the data are not shown in the tables. The patient was a man of fifty-three who

negative, was also treated with penicillin, with seemingly good results. The patient was a woman of thirty-eight who had severe rheumatic heart disease with mitral and aortic valvular disease but no congestive failure. She had persistent fever and some emboli before treatment, and after one of them she became comatose and developed a hemiplegia. In spite of repeatedly negative blood cultures, the patient was treated with penicillin—20,000 units intramuscularly every two hours for two weeks. She showed rapid and marked improvement, became afebrile and regained all functions, but has had repeated epileptiform seizures, probably the result of cerebral damage from the previous embolism. The patient had a splenic infarct during

TABLE 6. Autopsy Findings

CASE NO	RELEVANT FINDINGS	BACTERIOLOGY
8	Small, healing vegetations on aortic valve; large splenic abscess; brain and meninges normal.	Cardiac blood and vegetations,* no growth, splenic abscess; <i>Str. viridans</i> .
9	Large vegetations on aortic valve.	Cardiac blood, vegetations and spleen, <i>Str. viridans</i> .
12	Remnants of vegetations on aortic valve (ruptured cusp); healing leptomeningitis.	Cardiac blood, vegetations and meninges, no growth.
14	Vegetations on aortic and tricuspid valves; purulent leptomeningitis.	Spinal fluid, vegetations and lungs, <i>Str. haemolyticus</i> (Group A).
15	Vegetations on aortic and mitral valves; ruptured aortic cusp.	Cardiac blood, no growth; vegetations, gonococci
16	Vegetations on mitral valve; leptomeninges appeared normal	Cardiac blood and meninges, no growth; vegetations, nonhemolytic coagulase-negative <i>Staph. aureus</i> .

\*A few organisms were seen in direct smears.

had had symptoms of infection with changing murmurs but no embolic phenomena for two months before penicillin was begun. He had received sulfonamides without benefit and had three positive blood cultures for *Str. viridans* after this treatment was stopped. He had a systolic murmur at entry and developed a mitral diastolic murmur and enlargement of the spleen while under observation. Blood cultures taken eight hours after the first dose of penicillin and many later ones were all negative. He developed marked congestive failure and severe cerebral symptoms on the second day of penicillin therapy after showing considerable improvement. Thereafter his condition grew steadily worse, and he died of a cerebral embolus on the fifteenth day of treatment after receiving 4,500,000 units of penicillin. At autopsy there were the remains of a vegetative endocarditis of the mitral valve with erosion of most of the chordae tendineae, the stubs of which were hanging loosely. The lower third of the spleen was completely infarcted and necrotic, and there were other infarcts in the rest of the spleen and in the kidneys. Cultures of the heart blood showed no growth, but *Str. viridans* was grown from the vegetation and from the necrotic material in the spleen. The sensitivity of these organisms to penicillin was the same as that of the original blood-culture strain.

*Endocarditis with negative cultures.* An additional case that was probably one of subacute bacterial endocarditis, in which severe embolic phenomena occurred but all the blood cultures were

the third week after treatment ended but for three months has had no evidence of active infection.

#### CASES OF ACUTE BACTERIAL ENDOCARDITIS

A few apparent cures in cases of acute bacterial endocarditis treated with penicillin have been reported, but in most cases the treatment was unsuccessful.<sup>13-16, 23-26</sup> The diagnosis is difficult to make with certainty during life. It is strongly suspected, however, in cases in which there is persistent bacteremia without an obvious focus or after apparent improvement following a bacterial infection, when there are embolic phenomena and when cardiac murmurs appear for the first time and persist or change rapidly in character under observation. Brief résumés of 4 proved and 3 suspected cases are presented here. The significant data are shown in Tables 1 through 6. The cases will be considered, for convenience, according to their bacterial etiology.

*Pneumococcal endocarditis.* There were 2 cases in which pneumococcal bacteremia persisted following pneumonia in spite of sulfonamide therapy. In these cases the possibility of pulmonary thrombophlebitis must be considered in the differential diagnosis. The first of these (Case 10, Fig. 10) was that of a thirty-five-year-old man who had rheumatic heart disease with mitral insufficiency and was apparently well compensated. He had persistent Type 7 pneumococcus bacteremia following temporary improvement under sulfadiazine and then developed petechiae in the conjunctivas and

least a few days. In most cases in which the treatment was carried out for a long enough period, it has not been possible to culture the bacteria from the blood for variable periods after the treatment was discontinued. The proper dosage and duration of treatment have not yet been determined, but the present findings and those of many other writers suggest that in cases of *Str. viridans* endocarditis and probably also in cases due to other organisms it is necessary to give large doses for a fairly long period in order to obtain the most beneficial results.

The bacteria-free and symptom-free interval in each of the surviving cases is shown in Table 1. The results in Cases 6 and 7, in which there seemed to be a favorable response to the recurrent infection, suggest that these patients might have obtained a better result had the first course of treatment been continued with full doses for a longer period. On the other hand, the bacteriologic findings raise the question whether these recurrences represent new infections or relapses of the original infection. In Case 16, the differences in the characteristics of the staphylococcus originally obtained from the blood culture and of the one grown from the vegetation are also of interest in this regard, particularly since the latter was somewhat more susceptible to penicillin than the former and the patient had been treated for sixteen days. The findings in this case likewise suggest the possibility that earlier and more intensive treatment might have been more effective.

The significance of the penicillin concentrations in the blood and their relation to the susceptibility of the organisms are not entirely clear from the limited studies in the present cases. In some cases the clinical response seemed to be accelerated when the dosage was adjusted to maintain continuously a concentration higher than that necessary to inhibit the growth of the patient's organism. In others, however, similar or even better clinical results were apparently obtained in spite of the fact that adequate concentrations were maintained only during part of the interval between injections. The crudeness of the methods used may account in part for these discrepancies. It is interesting to note that while the patients were in congestive failure and on a limited fluid intake, somewhat smaller doses were usually required to maintain adequate blood concentrations.

Many factors probably influence the outlook for successful treatment with penicillin in cases of bacterial endocarditis. The susceptibility of the organism is only one of them. The amount of damage already done to valves and other structures has an important influence. Congestive failure developing or progressing rapidly, either before or during the course of treatment, is another significant factor. Obviously if valve cusps, chordae tendineae or septal structures have already been eroded, the elimination of further infection will not necessarily

result in any functional repair. The amount of damage already sustained by other vital organs is also a factor. All these points demonstrate the need for early diagnosis and early intensive treatment. Because of the more rapid course in cases of acute bacterial endocarditis, once this condition is established, it is particularly important to treat all patients who have persistent bacteremia as though they had potential cases of endocarditis.

Careful management of convalescence in so-called "arrested" or "cured" cases of subacute bacterial endocarditis is also necessary, and this is probably equally true in cases of endocarditis due to other bacteria. Embolic phenomena may occur for some time after the blood becomes bacteria-free. Each such occurrence carries with it the threat of further damage to valves or other underlying structures in the heart from which the emboli are released, as well as possible injuries where they become lodged. Severe cardiac failure may follow these occurrences. Reasonable treatment should therefore include a regime similar to that used in the care of cases of acute coronary thrombosis. This regime comprises an adequate period of inactivity to permit repair, followed by a very gradual increase in activity well within the limits of the cardiac reserve. The length of the convalescent period depends on an estimation of the cardiac status before and after treatment, the return of the white-cell count and sedimentation rate to normal and the possible occurrence of complications and embolic phenomena.

Infected foci in abscessed teeth, diseased tonsils and so forth should be eliminated. It is suggested that a course of treatment with penicillin or sulfonamides or both be begun just before tonsillectomy or tooth extractions and continued for a brief period thereafter, it being assumed that the original site remains vulnerable to reinfection with bacteria that may be released at the time. The finding at autopsy of infected abscesses at the site of splenic infarcts further suggests that a similar course of therapy would be advantageous immediately after any embolic manifestations in spite of the finding of negative blood cultures at such times. There may still be viable organisms in the embolus and at the site from which it was released.

Details of the autopsy findings are to be reported separately. Evidence of some healing was found in every case in which penicillin was given for a few days. In these cases, however, the amount of damage in the heart was usually sufficient to account for the cardiac failure.

Heparin was used in 5 cases of the present series. At first it was thought that the heparin was responsible for the occurrence of petechiae and emboli soon after the treatment was begun. The possible value of effectively eliminating the vegetation at the time when the antibacterial therapy was being carried out was considered as an advantage of the heparin. Subsequent observations in other cases of this series

Stokes respirations. At that time new and louder to-and-fro murmurs were heard, and the patient died a few hours later. At autopsy there were remnants of an acute vegetative endocarditis of the aortic valve, with rupture of one of the cusps where the vegetations had eroded the endocardium before they broke off. There was no gross evidence of meningitis. Cultures of the vegetations, cardiac blood and meninges showed no growth.

*Hemolytic streptococcus endocarditis.* Two patients with beta-hemolytic streptococcus endocarditis were treated with penicillin. One of them (Case 14) died after only two intramuscular injections. Cultures of the blood taken before treatment as well as those of the cardiac blood and vegetations at autopsy yielded a Group A streptococcus that did not react with available typing serums.

The other patient (Case 13, Fig. 13) was found to have a Group A, Type 28, hemolytic streptococcus bacteremia three weeks after what was probably

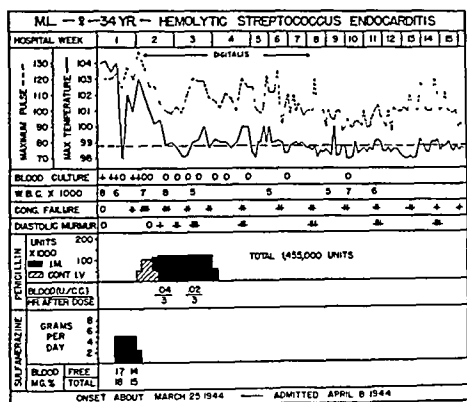


FIGURE 13. Case 13.

Persistent bacteremia followed what was probably a septic abortion and persisted during a short course of sulfamerazine. The patient developed congestive failure, which increased soon after penicillin treatment was started, and later a diastolic murmur appeared and persisted. The patient is now fully compensated and does not require digitalis.

a septic abortion. The bacteremia persisted under treatment with full doses of sulfamerazine. The patient had no known antecedent heart disease, but she developed congestive failure before penicillin was started, and this became steadily worse during three days of treatment given by constant intravenous infusion. Treatment was therefore changed to intramuscular injections, 15,000 units every three hours being sufficient to maintain bacteriostatic levels for the patient's organism. Blood cultures taken twenty-four hours after penicillin treatment was begun and all subsequent ones showed no growth. A loud aortic diastolic murmur was heard for the first time on the fifth day of penicillin treatment and persisted thereafter. The patient improved steadily, however, and the heart has gradually become fully compensated so that she is now able to carry on her usual activities without digitalis.

*Gonococcal endocarditis.* One patient (Case 15) was treated briefly and without success. She was a twenty-year-old woman in the sixth month of pregnancy who had an acute gonorrheal infection treated with sulfonamides five months before admission to the hospital. For four weeks she had had symptoms of a systemic infection. She developed petechiae, joint involvement and positive blood cultures for gonococcus and was then treated with sulfamerazine. Subsequent blood cultures were negative but fever persisted, and after two days of sulfonamides she was started on penicillin — 15,000 units intramuscularly every three hours. Shortly thereafter, however, she developed marked congestive failure and died after only three days on penicillin therapy. At autopsy there were vegetations on the mitral and aortic valves and one of the cusps of the latter had ruptured. Cultures of the cardiac blood yielded no growth, but gonococci were obtained from cultures of the vegetations.

*Staphylococcal endocarditis.* A fifty-two-year-old man (Case 16) was admitted to the hospital on the third day of an acute febrile illness during which he developed signs and symptoms of meningitis. At the time of entry he also had a generalized petechial and purpuric rash resembling that of meningococcemia, but these lesions later became pustular. A single dose of 5 gm. of sodium sulfadiazine was given on entry, and he was then treated with penicillin intramuscularly in the doses shown in Table 3. He was also given intrathecal injections of 15,000 units of penicillin twice the first day and then once daily for a total of nine injections. Spinal-fluid cultures were sterile on the third day, and blood cultures were negative on the fifth day. The symptoms of meningitis cleared slowly, and the patient became rational on the fifth day. He then developed gradually increasing congestive heart failure, which did not respond to the usual therapeutic measures, and a mitral systolic murmur was heard for the first time. He died after sixteen days of penicillin therapy. At autopsy the meninges appeared to be grossly normal, but there was a vegetative endocarditis of the mitral valve. Cultures of the cardiac blood and meninges gave no growth. Cultures of the vegetations yielded *Staphylococcus aureus* that was nonhemolytic, coagulase-negative and somewhat more sensitive to penicillin than the original blood-culture strain.

#### COMMENT

The results of the observations presented, when viewed in the light of the data already known and many that have not yet been published, indicate that penicillin is by far the most effective agent now available for the treatment of subacute bacterial endocarditis and for endocarditis caused by other susceptible organisms. It has rendered the blood stream free of bacteria in almost all such cases in which it has been given in adequate doses for at

## CLINICAL NOTE

### A NEW POCKET PRISMATIC MICROSCOPE

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A NEW compact microscope is shown in Figure 1. This pocket microscope weighs 1 pound and 6 ounces, and measures  $4\frac{1}{2}$  inches in length,  $2\frac{1}{2}$  inches in width and  $5\frac{1}{4}$  inches in height. Conventional eyepieces and objectives (low-dry, high-dry and oil immersion) are used, giving a magnification and size of field comparable to the ordinary laboratory microscope. The action of a large microscope is made possible in this diminutive model by bending the light rays through four right-angle prisms in line. A focal length of 175 mm. is maintained, and this allows the use of regular objectives and eyepieces. There is no appreciable loss of magnification or clarity.

This workshop model possesses only a coarse focal adjustment, but a fine adjustment can be added to the precision-built, factory instrument. There is some inevitable reflectionary loss of light as the rays pass through the prisms, but a similar loss of light occurs in the large binocular microscopes. The substage condensing of light, normally done with an Abbé condensing lens, has been practically accomplished by using a mirror of short focal length

(5-cm. radius and  $+10,-10$  curve) that reflects a completely satisfactory cone of light on the slide. The occasional desire for the reduction of light

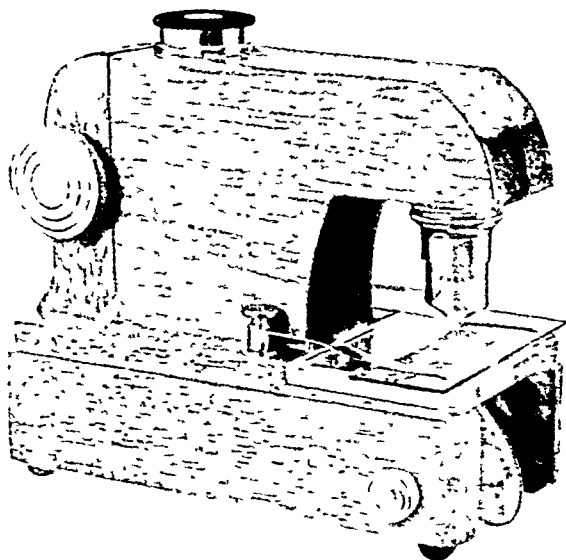


FIGURE 1.

usually accomplished with a diaphragm is performed by a mirror adjustment by means of a small knoblike button at the side of the base.

This prismatic microscope is presented as a small, light, powerful instrument for bedside use.

78 Washington Avenue

## MEDICAL PROGRESS

### THE CLINICAL IMPORTANCE OF THE RH BLOOD TYPE (Concluded)\*

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#### RH INCOMPATIBILITY IN PREGNANCY

In contrast to the type of mild or only moderate transfusion reactions described above in men and in nongravid women, it has been recognized for several years that during pregnancy, or shortly thereafter, women may have severe transfusion reactions when given presumably compatible blood during a first transfusion. In 1939, Levine and Stetson<sup>40</sup> reported a case of intragroup agglutination in a pregnant woman in which they demonstrated an abnormal agglutinin; they suggested that this had resulted from sensitization of the mother to some agent present in the fetus, inherited

from the father. They did not give this antigen a name, and only later recognized it as similar to the Rh factor described by Landsteiner and Wiener.

A typical instance of this sort is illustrated in the following case.

**CASE 4. Hemolytic reaction to first transfusion of Rh+ blood.** A 26-year-old woman at term in her third pregnancy gave the following history. The first pregnancy had resulted in a normal child, and the second, in an infant with moderate jaundice shortly after birth and anemia lasting 6 weeks. Recovery occurred without transfusion. Shortly before admission, fetal activity ceased, and a few hours later a still-born infant was delivered. At necropsy the diagnosis of erythroblastosis fetalis was substantiated.

There was considerable post-partum bleeding; this was uncontrolled by vaginal packing so that transfusion was necessary. The husband, being Group O and apparently compatible, was used. After 300 cc. of blood had been infused the patient showed signs of shock and passed a small amount of bloody urine. Thereafter her condition was precarious, with the development of anuria and jaundice. No further transfusions were given, and the patient recovered in about 3 weeks. Impaired renal function persisted, however.

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and those made by other workers have shown a similar course under treatment with penicillin alone. No advantage has therefore been found to justify the additional effort and risks of heparin treatment. A true evaluation of the relative merits of the combined treatment is extremely difficult and requires a considerably greater experience than is represented in the present series.

### SUMMARY AND CONCLUSIONS

The relevant data are presented in 9 cases of subacute bacterial endocarditis that were treated with sodium penicillin at the Boston City Hospital during 1944. The dose generally used was 25,000 units intramuscularly every two hours for two weeks. Seven of the patients are alive and have been free of evidences of active infection for one to eleven months.

Two patients had recurrence of infection, one after four months and the other after only one month. It is not certain whether these recurrences represent reactivation of the original infection or reinfection.

An additional fatal case of *Streptococcus viridans* endocarditis was treated. Another extremely severe case with a characteristic clinical course of subacute bacterial endocarditis with multiple emboli improved, and the patient was living three months after treatment, but no bacteria could be grown from the blood before penicillin was started.

All the fatal cases had severe heart failure resulting from extensive damage to cardiac structures.

The findings in 7 cases of acute bacterial endocarditis treated during the same period are also presented. Small doses were generally used in these cases because of the greater susceptibility of the organisms. In 3 of these cases, — one caused by a Type 7 pneumococcus, the second by a Type 5 pneumococcus and the third by a Group A, Type 28, hemolytic streptococcus, — the patients are living and well. The diagnosis in all the fatal cases was confirmed at autopsy but in those who survived is only highly probable.

Heparin was used together with penicillin in 3 of the *Str. viridans* cases and in 2 of those due to pneumococcus. There appeared to be no benefit from this therapy to justify the additional effort and risk.

The present findings suggest that early and intensive treatment with penicillin maintained for an

adequate period offers the best hope for recovery or arrest of infection in cases of subacute and acute bacterial endocarditis. The optimum dosage and duration of treatment are yet to be determined.

The importance of early diagnosis and treatment, as well as the careful and intelligent management of the convalescent phase, are stressed.

We are indebted to the members of the visiting and resident staff of the hospital, who co-operated generously in the study of these cases. The routine bacteriologic studies were done by Miss Marion E. Lamb and her associates at the Mallory Institute of Pathology.

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though Rh+, because the pregnancy initiates the stimulation of the mother's antibody production. In this case, previous transfusion caused antibody development, and even the first child suffered from severe erythroblastosis fetalis. Succeeding pregnancies with Rh+ infants resulted in similar catastrophes.

Erythroblastosis fetalis resulting from sensitization produced by the transfusion of an Rh- woman with Rh+ blood is always the worst form of this disease. Thus, in the 25 women in our series, 18 had two or more infants with erythroblastosis fetalis. Of 32 of these fetuses or babies, 28 died in utero, and 4 lived for less than twenty-four hours. Three women each had a single normal infant, and each of the latter was Rh-. In such cases, the sensitization may be established long before pregnancy begins, so that the Rh+ fetus begins to suffer harm early in gestation, probably from about the eighth to tenth week, when its red cells first develop Rh agglutinogens. Such infants are prone to die in utero, usually in the seventh to eighth month of gestation, and even those that are born alive, usually before the end of term, succumb within a day or two. Although this complication of pregnancy may occur relatively infrequently, it represents a major catastrophe in the life of such women and in their child-bearing potentialities. Only women married to heterozygous Rh+ men will succeed in having living children, and these will be Rh-. Since 38 per cent of the population is R+ homozygous, sensitization of the Rh- woman of child-bearing age by transfusion of Rh+ blood remains a serious hazard.

Because of the increasing use of stored blood and the frequency of transfusion as a therapeutic measure, the danger of immunization of women of child-bearing age is an increasing one. A recent development that makes this danger even greater is the use of resuspended red cells from which the plasma has been removed for the production of plasma. Since these cells have been made readily available in many large cities, especially on the public wards of hospitals, transfusion of resuspended cells has been liberally used. Since many women of child-bearing age have been given such blood without preliminary typing of the recipient for the Rh factor, the danger of sensitization with Rh+ cells has increased and the successful termination of future pregnancies has thereby been jeopardized, and needlessly so. Rh typing is therefore an important preliminary to the transfusion of women, particularly those in the child-bearing age.

#### ERYTHROBLASTOSIS FETALIS

This disease has already been mentioned as a sequel to sensitization of the Rh- mother to Rh+ red cells, with the development in the mother's serum of anti-Rh agglutinins. These can readily pass the placental barrier and affect the Rh+ infant

just as soon as a sufficiently high titer has developed in the mother's blood. This important discovery, the outstanding contribution to our understanding of erythroblastosis fetalis, was first made by Levine, Katzin, and Burnham<sup>41</sup> in 1941. It was proved conclusively in numerous subsequent studies by Levine and his co-workers,<sup>42-45</sup> and this has been confirmed by many others.<sup>46-50</sup> The disease usually develops in the second or subsequent Rh+ infant, since it usually requires at least one pregnancy to initiate sensitization of the Rh- mother, when a second or subsequent pregnancy restimulates her to the development of stronger agglutinins. Sometimes the first child to be so affected develops relatively mild symptoms of jaundice and anemia and recovers spontaneously.

The classic symptoms and signs of this disease are jaundice within twenty-four to forty-eight hours and the development of anemia, often at birth but more regularly by the third or fourth day, becoming most profound by the end of the seventh or the eighth day if the disease is not of the fulminating type. Death due to anemia and anoxia, however, may occur within the first twenty-four to forty-eight hours. Splenomegaly and hepatomegaly are quite frequently present. Edema and even universal hydrops may be noted in the most severely affected infants immediately after birth or within the first day. A large number of nucleated erythrocytes often occur in the peripheral blood, but this finding is not necessarily a criterion of the disease. Finally, erythroblastosis may develop in infants who do not have hemolytic anemia due to Rh incompatibility, especially those with infection, with congenital malformations of the heart, with anoxia due to atelectasis of the lungs and with intracranial hemorrhage, and even extremely premature infants. In the usual case, the final laboratory confirmation of the diagnosis is the demonstration of an Rh- mother, an Rh+ father, an Rh+ infant and anti-Rh agglutinins in the mother's serum.

In the severe forms, the jaundice often increases rapidly and is then augmented by an obstructive jaundice, owing to blockage of the bile capillaries in the liver and a disturbance of function of the hepatic cells. This obstruction may be so intense, with all the signs and symptoms so overshadowing the anemia and other signs of erythroblastosis fetalis, that the patient is thought to be suffering from congenital obliteration of the bile ducts. In fact some patients with hemolytic anemia have been subjected to exploratory operation for such a congenital defect before the diagnosis of hemolytic anemia was made.<sup>51, 52</sup> Hemolytic anemia of the newborn tends to become severer in succeeding pregnancies, with greater degrees of jaundice and earlier intrauterine death of the infant, with universal hydrops and anemia.

Treatment of the condition consists chiefly of the early recognition of the disease and the use of trans-



Blood typing revealed that the patient was 'Group 0, Rh-; her husband, Group 0, Rh+; and the two living children, Group 0, Rh+. The patient's serum showed a large amount of anti-Rh agglutinin.

In contrast to the forewarning that usually occurs in transfusion reactions due to Rh incompatibility in men or in nongravid women, in whom the first transfusion is uneventful and only the second may produce signs of a hemolytic reaction, in pregnancy the first transfusion given to the Rh- woman who has had an infant with jaundice, anemia or other signs of hemolytic anemia or erythroblastosis fetalis may result in a serious if not fatal reaction. In such cases it is found that the husband and the child are Rh+, that the mother is Rh- and that her serum contains anti-Rh agglutinins. As has been pointed out by Levine, a modified compatibility test will occasionally give warning of such an incompatible transfusion, in that the donor's cells may be agglutinated by the recipient's serum after incubation for half an hour at 37°C. This test when negative, however, cannot be relied on as evidence of no danger of a transfusion reaction, since, as has been pointed out, the test-tube agglutination method fails in more than 50 per cent of the persons in whom such antibodies are present.

A carefully taken history of the previous pregnancies, with the result of each, may occasionally forewarn of the danger of an intragroup transfusion reaction in women who have borne one or more children. In such cases a story of jaundice or anemia in a child or of a late stillbirth should always be regarded as significant, and the danger of a transfusion reaction should be avoided by careful grouping, Rh typing and cross-matching.

In contrast to the statistics for hemolytic transfusion reactions in men and nongravid women, severe reactions due to Rh incompatibility occur when immunization is the result of pregnancy. Thus, in 32 cases, 21 patients had moderately severe reactions and 6 had severe reactions, 5 of the latter dying. Such evidence alone is sufficient proof of the danger of transfusion in obstetric patients who are Rh-.

Another and even more serious type of reaction in pregnancy is illustrated below.

**CASE 5. Hemolytic reaction to second transfusion of Rh+ blood.** A 36-year-old patient had had four pregnancies, the first three children being alive and well and the fourth having died of prematurity and pulmonary atelectasis after 7 months of gestation. The fifth pregnancy was terminated by cesarean section at 7 months on account of a complete placenta previa, and the infant succumbed to atelectasis. The mother required a transfusion, the blood being obtained from the husband, a presumably compatible donor, later proved to be Rh+; no reaction followed. A sixth pregnancy four years later resulted in the precipitate delivery at 8 months of an infant with erythroblastosis fetalis, who died in 12 hours. The placenta was large, and there was considerable hydramnios.

Immediately after delivery continued bleeding from a hole in the uterus necessitated hysterectomy. Because of a hemorrhage, 500 cc. of presumably compatible blood (Donor 1) was given while the patient was still anesthetized. This was followed by a hematemesis and symptoms of shock. In the

following 3 hours three more transfusions (Donors 2, 3 and 4) were administered, with increasing shock, anuria and jaundice. Finally, transfusions from Donors 5, 6 and 7, especially chosen for their Rh type, were given with no untoward reaction. Anuria continued, however, and the patient became uremic and died in about 2 weeks.

Blood typing proved the patient was Group 0, Rh-; the husband, Group 0, Rh+, the children, Group 0, Rh+, Donors 1, 2, 3 and 4, Group 0, Rh+; and Donors 5, 6 and 7, Group 0, Rh-. The patient's serum contained a high titer of anti-Rh agglutinins when tested after the later transfusions. This Rh- woman, married to an Rh+ man, had three normal Rh+ infants. No sensitization occurred due to these pregnancies, as proved by the necropsy examination of the fourth and fifth infants and the uneventful transfusion of Rh+ blood following the fifth pregnancy. This transfusion, however, produced sensitization to the Rh factor, with the development of agglutinins. The sixth pregnancy probably increased the sensitization. The fetus was severely damaged by the agglutinins present in the mother's circulation and died of erythroblastosis. The several transfusions that were required produced serious hemolytic reactions, even though they were from homologous donors. Later typing proved that the reactions were due to the interaction of the infused Rh+ cells with the high-titered anti-Rh agglutinins in the patient's serum. Despite three compatible transfusions of Rh- blood, taken without reaction, the patient succumbed. Thus, although the pregnancies had produced no sensitization, a single transfusion of Rh+ blood sensitized the patient, with resulting harm to the next Rh+ fetus and to herself after transfusion of Rh+ blood.

Since some of the earliest symptoms of incompatible blood transfusion are subjective, it is generally advisable to avoid the use of whole blood in anesthetized patients.

In Rh- women sensitized by previous transfusion and in whom this sensitivity has been increased by pregnancy with an Rh+ fetus, transfusion reactions are almost invariably fatal, with, in addition, erythroblastosis producing death of the fetus before term. This was true in all 3 such cases in our series.

The last important complication of Rh incompatibility in pregnancy is the development of erythroblastosis in the fetus as the result of sensitization of an Rh- woman by transfusion of Rh+ blood. The following case is illustrative.

**CASE 6. Erythroblastosis fetalis resulting from incompatible transfusions.** A 23-year-old white woman gave the following history. At the age of 16 she had had a major operation for removal of a tumor and, because of subsequent bleeding, had required six blood transfusions, which were given without reaction. Two years later the recurrence of bleeding following surgery required four further transfusions. These produced no serious reactions, but the patient apparently felt uncomfortable and subsequently failed to show the expected rise in hemoglobin level. One year later, her first pregnancy ended at term in a stillborn infant with the congenital hydrops type of erythroblastosis fetalis.

Blood typing proved the patient to be Group 0, Rh-, and the husband, Group 0, Rh+. Two of the donors previously used were Rh+. The patient's serum contained a high titer of anti-Rh agglutinins. The following year, and again two years later, pregnancies resulted in stillborn infants with severe erythroblastosis of the fetal hydrops type.

This Rh- woman received multiple transfusions, which caused the development of a high titer of anti-Rh agglutinins. Her Rh+ husband transmitted this factor to his offspring. The usual history obtained in women having infants with erythroblastosis states that the first child is unaffected, even

satisfactory titer of agglutinins, but 4 developed none at all and showed no reaction at the end of a series of injections when given a larger amount of Rh+ blood. It remains for statistical studies, particularly those on men in the armed forces, where large amounts of whole blood have been given, to determine how many persons can develop anti-Rh agglutinins as the result of stimulation by transfusion alone. With the increasing therapeutic use of whole blood and its greater availability in blood banks, the Rh factor has become increasingly important.

Regarding pregnancy, it must first be realized that not every Rh- woman married to an Rh+ man will suffer harm from pregnancy with Rh+ infants. Owing to the occasional newspaper report of the birth of infants with erythroblastosis fetalis and the peculiarities of the mother's blood that produced such disturbances, flurries of excitement have occurred, and many women have been forewarned that, because they have Rh- blood, their pregnancies are sure to suffer forever after. Statistically the marriage of an Rh- woman to an Rh+ man occurs in 12 per cent of all marriages. Erythroblastosis fetalis has been stated to occur about once in two hundred deliveries (Javert<sup>73</sup> and Schwartz and Levine<sup>74</sup>), but was found as frequently as once in about one hundred and fifty deliveries in our series. Therefore, only one in about fifteen marriages between an Rh- woman and an Rh+ man will lead to erythroblastosis fetalis in the offspring, and this usually does not occur until the second or later pregnancy. In addition, the factors in isoimmunization by pregnancy alone can be resolved further on the basis of whether the father of the child is homozygous, that is, the offspring of two Rh+ parents, and carrying two Rh+ genes, or heterozygous and carrying only one Rh+ gene in his cells. This is not always detectable by Rh testing of his cells but is of practical importance. In the former case, all the children must be Rh+, although heterozygous; in the latter case, half the children will be Rh- and will thus escape harm by the agglutinins of the mother if such have developed through previous transfusion or pregnancy. In addition, to produce erythroblastosis fetalis, it is assumed that the placental barrier must be faulty and that the fetal Rh+ cells must be able to enter the maternal circulation.

Since the placental barrier is assumed to hold back cellular elements, since some persons do not respond to Rh antigen by anti-Rh production, since 49 per cent of Rh+ men are heterozygous and can father Rh- children and since two or more pregnancies are usually necessary to produce infants suffering from erythroblastosis fetalis, this disease remains a fairly rare complication of Rh differences between mates. It may even be suggested that other incompatibilities between man and wife are more hazardous to married life than differences in the Rh factor.

In attempting a prognosis for further pregnancies in any given family, it is of value not only to test the mother's blood for anti-Rh agglutinins in the second and subsequent pregnancies, but also to try to determine whether the father is homozygous or heterozygous. Should he be homozygous and one infant with erythroblastosis has been born, all subsequent infants will be similarly affected and further pregnancies may be contraindicated.

An additional laboratory measurement of prognostic value is the determination of the increase in anti-Rh titer during pregnancy in women who have had a previous infant with erythroblastosis fetalis or who have been sensitized by an Rh+ transfusion. In such cases, the agglutinin titer tends to increase relatively late in pregnancy, usually by the seventh or eighth month. Earlier in pregnancy, the presence of anti-Rh agglutinins has not been proved harmful to the fetus, since even a high titer of antibodies does not usually cause abortion at the second or third month of gestation. Possibly this is related to the relatively late appearance in the fetus of red cells carrying the Rh agglutigen. They have been found by us in a three-month fetus on four separate occasions, by Stratton<sup>75</sup> in a 48-mm. embryo and by Bornstein and Israel<sup>76</sup> in a 17-cm. fetus.

If the titer does suddenly rise, the delivery of an infant who seems large enough to be viable at about eight to eight and a half months of gestation results in a milder degree of erythroblastosis than if the infant had been permitted to remain in utero and thus subjected to a high titer of agglutinins until term. The following case is illustrative.

**CASE 7. Increase in anti-Rh titer during pregnancy.** A 30-year-old woman had had a normal first-born child and a second child who died of erythroblastosis on the 3rd day of life. The husband proved to be Rh+; the wife, Rh-; and the two children, Rh+.

During the third gestation, tests on the mother's serum for anti-Rh agglutinins were as follows: at 6 months, negative; at 7 months, negative; at 7½ months, low agglutinin titer; at 8 months, moderate agglutinin titer; and at 8½ months, high agglutinin titer. Because of the sudden increase in antibodies against the Rh factor late in pregnancy, delivery was induced at 8½ months, and a 5-pound, Rh+ infant was obtained. Within 24 hours, jaundice and anemia were noted, but after three transfusions the infant recovered and remained well.

In this case, although a second child had died at term of erythroblastosis, a third pregnancy resulted in a child surviving after several transfusions.

This is one of the two methods of proved value in assisting the previously sensitized Rh- mother to have a living Rh+ infant. In 41 cases of early induction of delivery on account of a rising titer of anti-Rh agglutinin, there have been 32 living and 9 dead children. The other method, particularly applicable in the mating of a homozygous Rh+ man to a sensitized Rh- woman, is artificial insemination using an Rh- donor. This has been uniformly successful in 6 cases. Potter and Willson<sup>77</sup> have recently reported a similar experience. The

fusions of compatible blood, which for the first ten to fourteen days of life should be Rh—. For this, the mother's washed cells or, still better, whole blood from an Rh— donor may be used.<sup>42, 53-57</sup> The rationale for the use of Rh— blood is that many of these infants still have in their circulation anti-Rh agglutinins that are not combined with their own Rh+ cells and are therefore potentially active against other Rh+ cells infused into the infant's circulation. Rh— cells cannot be affected by such abnormal agglutinins and have been proved to survive in the infant's circulation.<sup>52, 58</sup>

Infants with erythroblastosis should not be permitted to receive the mother's breast milk, since it has been proved that the agglutinins may be present therein and, after absorption through the stomach, may produce further destruction of the Rh+ cells.<sup>50, 59, 60</sup>

One of the complications of erythroblastosis fetalis of the severe icteric type (icterus gravis familiaris) is damage to the nuclei of the brain, a condition known as kernicterus. When this occurs, the infant exhibits convulsions, twitching, opisthotonos and respiratory difficulties. Death may occur in the first week. If the baby survives, he is sometimes left with an impaired nervous system, with spastic paraplegia and mental retardation later in life. Fortunately, this complication of the severely icteric type of erythroblastosis occurs in less than 16 per cent of all such patients. The majority of children who recover develop normally in later life and show no damage from the early hemolytic anemia. One late complication in infants who have been severely jaundiced at birth is a deep-green staining of the deciduous teeth. This is directly related to the degree and the time of the jaundice in intrauterine and neonatal life and is the result of pigment deposition in the growing enamel. It does not affect the permanent teeth and can therefore be ignored.

#### TESTING FOR RH FACTOR AND ANTI-RH AGGLUTININS

There are a few practical considerations regarding laboratory technics involving the Rh factor and anti-Rh agglutinins. In performing tests for the Rh factor, it is important to make certain that the red cells are obtained from freshly drawn blood. The Rh agglutininogen is apparently more fragile than are the A and B agglutininogens and tends to give weaker reactions the longer the red cells remain outside the body, particularly if they are suspended in normal saline solution; thus, false negative tests may result. The details of the technic of Rh testing, including the precautions necessary for accuracy, have been best described by Wiener,<sup>32</sup> by Levine<sup>61</sup> and by Taylor.<sup>62</sup>

The anti-Rh serum used for Rh determinations should be tested frequently against known Rh+ and Rh— cells. Such serum, especially if originally low

in potency, tends to deteriorate on standing, even when stored in the refrigerator. In general, the serum should be of the highest possible potency and of wide specificity. At least four types of serum have already been identified, namely, one that agglutinates only 30 per cent of Rh+ cells (anti-Rh''), one that agglutinates 73 per cent of Rh+ cells (anti-Rh'), one that agglutinates 85 per cent of Rh+ cells (anti-Rh<sub>0</sub>) and one that agglutinates 87 per cent of Rh+ cells (anti-Rh). For complete differentiation, more than one of the first three serums may be necessary.

It has been advised that the demonstration of anti-Rh agglutinins be carried out in the test tube with a dilute suspension of Rh+ cells from a known donor and freshly drawn serum from the subject under investigation.<sup>32, 53, 61-65</sup> This test, however, is not always conclusive, since a new type of antibody, the so-called "blocking antibody" of Wiener,<sup>66</sup> the "incomplete antibody" of Race<sup>67</sup> or the "inhibitor substance,"<sup>68</sup> is present in more than 50 per cent of the serums of women who have been sensitized by transfusion or pregnancy, or both; this inhibits agglutination of a dilute suspension of Rh+ cells by anti-Rh agglutinin in a test tube on incubation at 37°C. Wiener has suggested a test for this blocking antibody. Furthermore, a rapid method for the demonstration of anti-Rh agglutinins that avoids difficulties resulting from the inhibitor substance has been described.<sup>69</sup> It must therefore be recognized that anti-Rh agglutinins may exist in the serum of sensitized persons without necessarily being demonstrable by the test-tube incubation method of detection and that the so-called "modified compatibility test" cannot be used as the sole safeguard in cross-matching preliminary to transfusion.

#### PRACTICAL APPLICATIONS

That the determination of the Rh factor has practical value has been briefly presented in the preceding pages. More comprehensive reviews have been written by Potter,<sup>70</sup> by Davidsohn<sup>71</sup> and by Boyd.<sup>72</sup> From the accumulated facts, certain conclusions are permissible.

It is of increasing importance that recipients of transfusions, especially of multiple transfusions, be typed for the Rh factor. The Rh— individuals (13 per cent of the white population) who receive Rh+ blood may develop anti-Rh agglutinins, which will interfere in succeeding transfusions with complete benefit from the infused blood. Transfusion reactions of increasing severity will then occur, and in some cases these may cause serious kidney damage, although death does not commonly occur as a result of Rh sensitization from transfusion alone. An attempt to evaluate the frequency with which men or nongravid women can develop anti-Rh agglutinins when given Rh+ cells was made by repeatedly injecting small amounts of such cells into Rh— subjects. Six of 10 men developed a

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31171

#### PRESENTATION OF CASE

A fifty-two-year-old man was admitted to the hospital because of difficulty in swallowing.

Six weeks before admission, the patient noticed difficulty in swallowing solids for the first time. He had to follow solid food with large amounts of tea and other liquids, otherwise hiccoughs and slight substernal pain ensued. This difficulty progressed, and an uncomfortable "stretching sensation" with each swallow became pronounced about the area of the midsternum. Over a period of four weeks the dysphagia became so marked that he could swallow only liquids and mushy foods. He had no nausea or regurgitation and had lost little or no weight. He felt well and did not become fatigued easily. A barium swallow and chest x-ray in the Out Patient Department two weeks before admission showed the swallowing function to be normal. The esophagus was rather irregularly dilated to a point about 16 cm. above the esophago-gastric junction, where there was a constant narrowing with probable shelf formation extending for a distance of 7 cm. There was no ballooning in this area, and the barium passed through rather rapidly without evidence of obstruction. The mucosal pattern did not appear to be normal in this area, and there was probably a small amount of destruction. The remaining 9 cm. of esophagus appeared to be normal. Two weeks before admission the patient allegedly had one tarry stool. He had had frequent nosebleeds in the past few weeks and thought that he had regurgitated small amounts of blood. The patient believed that he had become quite pale in the past two years.

At twenty-two years he had had pneumonia, and in his early twenties gonorrhea. At twenty-five years of age he had suffered from migratory joint pains, was told that he had rheumatism and remained in the hospital for two months. The following year he had a tonsillectomy. He was seen frequently in the Out Patient Department at the age of forty-eight, four years before admission, because of severe substernal pain on exertion, which was promptly relieved by rest or nitroglycerin. X-ray

films at that time showed the heart to be enlarged across the base, with a prominent left auricle and pulmonary conus. The lung fields and diaphragm were normal. An electrocardiogram was thought to be within normal limits. The blood pressure was 120 systolic, 80 diastolic. The anginal pain improved, but he continued to be moderately dyspneic on exertion.

Physical examination revealed a slightly obese, well-developed man in no distress. The chest was moderately emphysematous, and a few inspiratory rales were heard at the apices. The apex beat was 1 cm. to the left of the midclavicular line. A loud first sound was heard at the apex. There was a questionable early diastolic murmur along the left sternal border in the third interspace. The aortic second sound was greater than the pulmonic. The abdomen was normal. There was no lymphadenopathy. A rectal examination revealed an enlarged, firm, smooth prostate.

The temperature and respirations were normal. The pulse was 75.

Examination of the blood showed a red-cell count of 5,160,000 and a white-cell count of 9200. Examination of the urine was negative. Stools were guaiac negative. The prothrombin time was 23 seconds (normal, 18 to 20 seconds). The serum nonprotein nitrogen, the protein and the chloride values were normal. An electrocardiogram showed normal rhythm at 85, a PR interval of 0.18 second, normal axis, small Q<sub>1</sub>, upright T<sub>1</sub>, T<sub>2</sub> and T<sub>4</sub> and flat T<sub>3</sub>.

X-ray films of the chest showed no evidence of metastatic cancer. There appeared to be some enlargement of the left auricle and perhaps of the left ventricle.

On the sixth hospital day the patient was esophagoscoped. The instrument passed readily to approximately 29 cm. below the teeth, where there was marked narrowing of the lumen to a diameter of approximately 3 mm. There were reddening, slight irregularity and erosion of the anterior wall. Seven hours after esophagoscopy the patient became slightly dizzy and cyanotic, with mild, nonradiating, substernal pain. The blood pressure was 60 systolic, 40 diastolic. The temperature was 100.6°F., and the pulse was irregular and thready, with a rate of about 110. The patient perspired profusely, became unresponsive and developed convulsive twitchings. A few seconds after oxygen was administered he regained consciousness. An electrocardiogram revealed auricular fibrillation, with a rate of 155, normal axis, low upright T<sub>1</sub> and upright T waves in Leads 2, 3, CF<sub>2</sub>, CF<sub>4</sub> and CF<sub>6</sub>. There were two ventricular premature beats in Lead 1. In some areas the P waves seemed prominent and suggested runs of paroxysmal auricular tachycardia. A repeat electrocardiogram three hours later was unchanged, except that the rate had increased to 175. Two hours after 6 cc. of Cedilanid had been given, the patient

\*On leave of absence.

emotional adjustments necessary for this form of treatment do not recommend it for widespread use.

### CONCLUSIONS

The Rh blood type, present in about 87 per cent of the white population, is of practical importance almost exclusively to the persons who lack it. In the latter, repeated transfusion of Rh+ blood cells may lead to increasing hemolytic reactions, owing to the interaction of anti-Rh agglutinins initiated by the first Rh+ transfusion with the specific agglutino-gen of the infused cells.

Rh- women married to Rh+ men may be sensitized by means of one or more pregnancies involving an Rh+ fetus, the Rh factor being inherited as a dominant trait. Although this only occurs in one of about fifteen such matings, once so immunized, the woman cannot safely be given even one transfusion of untyped or Rh+ blood, since it may produce a serious, even fatal, hemolytic reaction.

A single Rh+ transfusion to an Rh- woman, married to an Rh+ man, may initiate the antibody response, and a subsequent pregnancy with an Rh+ fetus may end in the severest form of erythroblastosis fetalis in the infant. Women of child-bearing age must therefore be protected against this potential danger.

Infants who have erythroblastosis fetalis should be treated early and actively with transfusions of Rh- blood. The diagnosis of the usual type of erythroblastosis fetalis is dependent not only on the well-known physical signs but also on the laboratory demonstration of anti-Rh agglutinins in the Rh- mother of an Rh+ infant of an Rh+ father.

The laboratory technics for testing for the Rh factor and anti-Rh agglutinins require certain safeguards and experience.

Finally, Rh typing is necessary for all recipients (male or female) of repeated transfusions, for all women requiring transfusion, to avoid serious reactions in those who have borne an erythroblastotic infant and to avoid sensitization of Rh- women of child-bearing age, for the listing of Rh- donors for emergency use and for the procurement of Rh- banked blood to be given to Rh- patients.

An anti-Rh determination is particularly indicated in pregnant women whose histories show that one or more previous pregnancies ended in late stillbirths, infants with severe jaundice or anemia or even infant deaths apparently due to hemorrhage or anoxia, in Rh- women who have received transfusions, especially from their husbands and in Rh- women married to Rh+ men who have had one or two children and may therefore have been sensitized to the Rh factor.

Some practical benefit may be derived from following the anti-Rh agglutinin titer of the serum during the pregnancy of the woman who has had a previous child with erythroblastosis fetalis.

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31171

#### PRESENTATION OF CASE

A fifty-two-year-old man was admitted to the hospital because of difficulty in swallowing.

Six weeks before admission, the patient noticed difficulty in swallowing solids for the first time. He had to follow solid food with large amounts of tea and other liquids, otherwise hiccoughs and slight substernal pain ensued. This difficulty progressed, and an uncomfortable "stretching sensation" with each swallow became pronounced about the area of the midsternum. Over a period of four weeks the dysphagia became so marked that he could swallow only liquids and mushy foods. He had no nausea or regurgitation and had lost little or no weight. He felt well and did not become fatigued easily. A barium swallow and chest x-ray in the Out Patient Department two weeks before admission showed the swallowing function to be normal. The esophagus was rather irregularly dilated to a point about 16 cm. above the esophago-gastric junction, where there was a constant narrowing with probable shelf formation extending for a distance of 7 cm. There was no ballooning in this area, and the barium passed through rather rapidly without evidence of obstruction. The mucosal pattern did not appear to be normal in this area, and there was probably a small amount of destruction. The remaining 9 cm. of esophagus appeared to be normal. Two weeks before admission the patient allegedly had one tarry stool. He had had frequent nosebleeds in the past few weeks and thought that he had regurgitated small amounts of blood. The patient believed that he had become quite pale in the past two years.

At twenty-two years he had had pneumonia, and in his early twenties gonorrhea. At twenty-five years of age he had suffered from migratory joint pains, was told that he had rheumatism and remained in the hospital for two months. The following year he had a tonsillectomy. He was seen frequently in the Out Patient Department at the age of forty-eight, four years before admission, because of severe substernal pain on exertion, which was promptly relieved by rest or nitroglycerin. X-ray

\*On leave of absence.

films at that time showed the heart to be enlarged across the base, with a prominent left auricle and pulmonary conus. The lung fields and diaphragm were normal. An electrocardiogram was thought to be within normal limits. The blood pressure was 120 systolic, 80 diastolic. The anginal pain improved, but he continued to be moderately dyspneic on exertion.

Physical examination revealed a slightly obese, well-developed man in no distress. The chest was moderately emphysematous, and a few inspiratory rales were heard at the apices. The apex beat was 1 cm. to the left of the midclavicular line. A loud first sound was heard at the apex. There was a questionable early diastolic murmur along the left sternal border in the third interspace. The aortic second sound was greater than the pulmonic. The abdomen was normal. There was no lymphadenopathy. A rectal examination revealed an enlarged, firm, smooth prostate.

The temperature and respirations were normal. The pulse was 75.

Examination of the blood showed a red-cell count of 5,160,000 and a white-cell count of 9200. Examination of the urine was negative. Stools were guaiac negative. The prothrombin time was 23 seconds (normal, 18 to 20 seconds). The serum nonprotein nitrogen, the protein and the chloride values were normal. An electrocardiogram showed normal rhythm at 85, a PR interval of 0.18 second, normal axis, small Q<sub>1</sub>, upright T<sub>1</sub>, T<sub>2</sub> and T<sub>4</sub> and flat T<sub>3</sub>.

X-ray films of the chest showed no evidence of metastatic cancer. There appeared to be some enlargement of the left auricle and perhaps of the left ventricle.

On the sixth hospital day the patient was esophagoscoped. The instrument passed readily to approximately 29 cm. below the teeth, where there was marked narrowing of the lumen to a diameter of approximately 3 mm. There were reddening, slight irregularity and erosion of the anterior wall. Seven hours after esophagoscopy the patient became slightly dizzy and cyanotic, with mild, nonradiating, substernal pain. The blood pressure was 60 systolic, 40 diastolic. The temperature was 100.6°F., and the pulse was irregular and thready, with a rate of about 110. The patient perspired profusely, became unresponsive and developed convulsive twitchings. A few seconds after oxygen was administered he regained consciousness. An electrocardiogram revealed auricular fibrillation, with a rate of 155, normal axis, low upright T<sub>1</sub> and upright T waves in Leads 2, 3, CF<sub>2</sub>, CF<sub>4</sub> and CF<sub>6</sub>. There were two ventricular premature beats in Lead 1. In some areas the P waves seemed prominent and suggested runs of paroxysmal auricular tachycardia. A repeat electrocardiogram three hours later was unchanged, except that the rate had increased to 175. Two hours after 6 cc. of Cedilanid had been given, the patient

was comfortable and oriented, with a strong, regular pulse, at a rate of 90, and a blood pressure of 105 systolic, 65 diastolic.

On the following day he passed about 300 cc. of dark blood by rectum. He became pale, and the red-cell count dropped to 3,300,000, and the blood pressure to 90 systolic, 60 diastolic, with a pulse of 90. He had mild substernal pain and coughed up a small amount of blood. He developed purpuric spots over his arms and legs (similar spots had allegedly been appearing and disappearing during the previous month).

X-ray films of the chest showed clear lung fields, with no air in the mediastinum. A repeat film on the eighth hospital day showed linear areas of increased density opposite the fourth rib anteriorly that were not present previously. Two subsequent films showed no change. On the eleventh hospital day the stools were tarry. The red-cell count had dropped to 2,600,000. A repeat prothrombin time was 23 seconds (normal, 18 to 20 seconds). A blood smear showed 84 per cent neutrophils, 10 per cent lymphocytes and 4 per cent monocytes, with almost no platelets and no abnormal red or white cells. A diagnosis of thrombocytopenic purpura was made. Several blood transfusions were given and a splenectomy was performed on the fifteenth hospital day. The patient was kept digitalized and made a prompt recovery. After several transfusions the red-cell count rose to 4,300,000. The bleeding tendency ceased, but the platelet count did not rise.

During the third hospital week the patient became hoarse. The hoarseness increased, and on the twenty-ninth hospital day the left vocal cord was found to be completely paralyzed. The temperature following splenectomy had had daily swings from normal to 100 or 101°F.

On the thirtieth hospital day, the temperature spiked to 104°F. and he began to have paroxysms of cough, during which he brought up bloody sputum. There was no pain; the blood pressure was 110 systolic, 60 diastolic, and the respiratory rate was 22. Dullness and diminished breath sounds developed in both lung bases. X-ray examination of the chest showed an extensive area of increased density close to the right side of the dorsal spine, as well as areas of increased density extending into both lung fields, more marked on the left than on the right. This had not been seen on the films taken two days previously. One swallow of barium was given and, before fluoroscopic observation was possible, the patient experienced a coughing spell, following which barium was seen to outline the previously described irregular mass in the esophagus and also the lower end of the trachea and both stem bronchi. A large amount of barium collected in an irregular cavity that was apparently connected with the esophageal mass and not with the bronchus (Fig. 1). The temperature and respirations remained elevated, and the cough became ineffective. On the

thirty-sixth hospital day he became semiconscious, coughed and vomited gross blood and finally went into shock and expired.

#### DIFFERENTIAL DIAGNOSIS

DR. EARLE M. CHAPMAN: May we see the x-ray films?

DR. GEORGE W. HOLMES: In this set of films there is nothing definite in the lungs or in the appearance of the heart. The esophagus shows no



FIGURE 1.

obstruction but has a peculiar appearance in the midportion. I do not know when these spot films were taken, but obviously there is a lesion at this point. There is no evidence of disease in the lungs or heart. To go back to the esophagus, there is an extensive filling defect in it, with some dilatation. It is not the annular infiltrating type of lesion that one ordinarily sees but has the appearance that one sees when there is something inside the esophagus, either a lobulated tumor mass or a foreign body, or both. Later on something happened that allowed the barium to pass from the esophagus into the bronchial tree (Fig. 1) and there is quite a different picture, which is now that of a fistula between the esophagus and the bronchial tree.

DR. CHAPMAN: The bronchial tree at the bifurcation lies on the anterior wall of the esophagus. What is the relation of the aorta at this level to these two structures?

DR. HOLMES: They are close to the ascending aorta.

DR. CHAPMAN: It seems to me that this patient died because of a lesion that was located in an area at the level of the bifurcation of the trachea and at the portion of the esophagus that we believe was 29 cm. down from the teeth. At the level of this eroding lesion there were several structures. We have to believe that it involved the trachea, the bronchi at the bifurcation and the anterior wall of the esophagus and the heart; the left and right auricle lie anterior to this, and the ascending portion of the aorta lies immediately behind. What sort of process would first cause trouble in swallowing and later lead to definite erosion? I should like to ask Dr. Holmes why there was no ballooning of the esophagus above the lesion.

DR. HOLMES: The esophageal wall was rigid and did not expand. A cancer can do that; of course there are other more unusual lesions.

DR. EDWARD B. BENEDICT: We see cancer frequently without obstruction and without much dilatation.

DR. CHAPMAN: It seems clear that this man had an eroding process in the esophagus. He was esophagoscoped, and from there on his course was an unhappy one; he went into shock and bled into the intestinal tract and also into the bronchial tree. The incident of cardiac disturbance might well have been from irritation of the sinoauricular node, which lies in the auricle at this same level. The disturbance of rhythm was controlled, and I do not believe that it indicates coronary occlusion.

DR. HOLMES: The descending aorta is seen fairly well, and if one can tell anything from examination of the x-ray films, he did not have an aneurysm of the aorta.

DR. CHAPMAN: If one can tell, but of course one cannot always tell.

DR. HOLMES: I thought it might help you.

DR. CHAPMAN: Many points suggest syphilis rather than carcinoma.

DR. HOLMES: I thought that you were working up to a differentiation of tumors and aneurysm and were assuming that there was more in the x-ray films than there is.

DR. CHAPMAN: I should like to know about the Hinton and Wassermann tests. There are many things that favor syphilis and I might as well discuss that diagnosis. The patient had angina four years before entry, and it cleared up considerably; this is unusual for ordinary angina, it is usually progressive. We are told that he had a blowing diastolic murmur along the left border of the heart. If we can accept that as a fact, it is strong evidence of a syphilitic lesion involving the heart and causing

aortic regurgitation. We know that he finally died from a process that eroded through into the bronchus and into the esophagus, so if it were an aneurysm it must have been in the descending aorta, a most unusual place. Is that correct, Dr. Holmes?

DR. HOLMES: Yes.

DR. CHAPMAN: This is likelier, however, to be a tumor. Where, then, did the primary tumor lie? With the x-ray description and the later description that it did not cause obstruction, one wonders if it arose from the heart and penetrated the esophagus, or if it arose at the bifurcation of the trachea or in the bronchial tree and was perhaps growing inward to the anterior wall of the esophagus. A good deal of blood had obviously leaked from the primary tumor into the lungs, and he had pneumonitis when he died. Even the barium, as you see, passed out into the lungs through the eroded area. Primary carcinoma of the esophagus has to be considered.

The appearance of purpura hemorrhagica or thrombocytopenic purpura, I believe, was symptomatic of the other process. Whether the main process was syphilis or carcinoma, it is obvious that splenectomy did not increase the platelets, so probably it was not a true thrombocytopenic purpura, which is followed by a rise in platelets after splenectomy.

What else do we have to consider?

In reading one of the x-ray descriptions I thought of pulmonary infarction because of the linear areas of density, but I do not believe that we have to consider such a diagnosis in this case. The disturbance of cardiac rhythm is interesting. I should guess that this man had a good deal of inflammatory reaction about the heart, which involved the surface of the auricles, and that this irritation set up a disturbance of rhythm.

What types of tumor do we have to consider other than carcinoma? It may be that this man's symptoms four years before entry, interpreted as angina, were mistakenly diagnosed. This assumption is supported by the normal electrocardiogram and by Dr. Holmes's statement that the heart was normal by x-ray. He might have had a benign lesion in the esophagus, such as a polyp, that was causing intermittent obstruction and symptoms simulating angina. The reason he got better is that the trouble was not cardiac or vascular in origin. I wonder if he had some unusual type of tumor, such as a hemangioma. All these are remote, however, and it is up to the pathologist to tell what type of tumor this man actually had. I regret the lack of a blood Hinton test, although I do not believe that the lesion was an aneurysm.

DR. RONALD C. SNIFFEN: There was a negative Hinton test reported in the record, which supports your argument against syphilis.

#### CLINICAL DIAGNOSIS

Carcinoma of esophagus.



## DR. CHAPMAN'S DIAGNOSES

Mediastinal tumor (? type), involving esophagus, bifurcation of trachea and auricles.  
Purpura, symptomatic.

## ANATOMICAL DIAGNOSES

Malignant lymphoma (clasmatocytic type) of esophagus and mediastinal and retroperitoneal lymph nodes.  
Esophagobronchial fistula.  
Purpura, symptomatic.  
Coronary sclerosis.  
Operative wound: splenectomy.

## PATHOLOGICAL DISCUSSION

DR. SNIFFEN: This man had a tumor that surrounded the esophagus, starting at the bifurcation of the trachea and extending downward for 11 cm. The mucosa of the anterior esophageal wall was destroyed over an 11-by-3 cm. area. Tumor also involved the mediastinal lymph nodes and had spread to the right lower lobe, eroding one of the secondary branches of the lower lobe bronchus. In doing this it had produced a fistula between the esophagus and the bronchus, with the result that a 12-cm. abscess had formed in the right lower lobe in its medial part, with satellite abscesses lateral to it. Tumor also involved the retroperitoneal lymph nodes behind the stomach and had ensheathed the arch of the aorta. Microscopic sections of this tumor showed a clasmatocytic lymphoma or, in other words, a reticulum-cell sarcoma.

In addition he had a widespread purpura of the skin, the mucous membranes of the small intestine and kidney pelvis and the pancreas. Two hundred centimeters of bloody fluid were found in each pleural cavity, and 100 cc. in the pericardial sac. The heart was not enlarged, but there were ecchymoses in the epicardium, in the endocardium of both ventricles and throughout the muscle of the septum and left apex. He had quite severe arteriosclerosis of the coronary arteries, but we could find no occlusion. The only indication of rheumatic heart disease was slight interadherence of the cusps of the aortic valve. The bone marrow was not involved by tumor; it was hyperplastic and contained only a few megakaryocytes. We know that purpura does occur in a small percentage of people with malignant lymphoma. I am not sure whether or not one has to have bone-marrow involvement to produce the purpura. We could find nothing abnormal in the resected spleen.

## CASE 31172

## PRESENTATION OF CASE

A seventy-five-year-old business executive was brought to the hospital after he had collapsed in the street.

He had had frequent medical checkups for the past twenty-five years and until about six months before admission had been active and well, with a blood pressure of 160 systolic, 90 diastolic. At that time he began to notice a feeling of pressure or aching in the upper sternal region during exertion. Four months later the pain was no longer present. During the past few months he had had nocturia (three or four times) and had been treated non-surgically for prostatic hypertrophy. On the evening before admission he noted a dull ache in the lumbar region of the back. Despite moderate discomfort he fell asleep but noticed the ache when he arose to urinate, as usual during the night and when he got up the following morning. He had an unusually small bowel movement that morning and passed urine without difficulty at noon. After breakfast he took a streetcar downtown. After an early noon lunch he walked into the street, whereupon the pain in the back became severe. He felt faint and collapsed, losing consciousness for a period of a few minutes. About ten minutes after he was brought into the hospital he vomited a large amount of gastric content, which contained no gross blood. Approximately half an hour later he vomited again and felt much relieved, although he still complained of slight pain in the back.

Physical examination showed a well-developed, well-nourished man in a state of collapse. The blood pressure was 80 systolic, 60 diastolic. The pulse was 94 and of poor quality. The neck veins were not distended. The apex beat could not be felt, and the heart sounds were very distant. There were no murmurs or gallop rhythm. The lungs were clear, and the abdomen was soft, with slight tenderness in the right lower quadrant; no masses could be felt. The liver and spleen were not palpable. A surgical consultant was impressed by an easily felt pulsation low in the left abdomen. This pulsation lay more laterally than one would expect, unless the aorta were displaced to the left. Good femoral pulsations were felt bilaterally. The dorsalis pedis and posterior tibial arteries could not be felt. The arms and legs were cool.

The oral temperature was 97°F; four hours later the rectal temperature was 100°F. The pulse and respirations did not change significantly.

Examination of the blood four hours after admission showed a white-cell count of 27,600, with 84 per cent neutrophils, 12 per cent lymphocytes and 4 per cent monocytes. Two electrocardiograms taken six hours apart showed no progression of change. Both showed normal rhythm, at a rate of 70 to 80, and marked left-axis deviation. There was slight depression of the ST segments in Leads 2 and 3, and very low T waves in Leads 1 and CF<sub>1</sub>, with diphasic T waves in Lead CF<sub>1</sub>; QRS was of a low amplitude in CF<sub>1</sub>.

The patient lay quietly in bed conversing amiably, in no pain. The pulse was strong. The abdomen

was flaccid, save in the right lower quadrant, where at first he was quite tender. After reassurance there was little spasm and extremely little tenderness. There was a soft, slightly fluctuant, nonpulsating mass, which gave the sensation of mobility that one gets with a large soft cyst or wadded loops of bowel. The easily felt pulsations low in the left abdomen were still present. Peristalsis was normal. He continued to have pain in the back and noted a slight pain down the anterior aspect of the right thigh. Shortly after the examination the patient suddenly sat up in bed, gasped and expired.

#### DIFFERENTIAL DIAGNOSIS

DR. ROBERT R. LINTON: The blood pressure was 160 systolic, 90 diastolic. That sounds like a fairly good blood pressure for a man of this patient's age. What do you think, Dr. Richardson?

DR. WYMAN RICHARDSON: It is an excellent blood pressure.

DR. LINTON: It seems to me that I have to decide why this man went into shock as he walked out into the street and, after a period of relatively few hours, suddenly died. I can think of four conditions that might explain his demise. Certainly something quite dramatic happened, as evidenced by his losing consciousness and the reduction in blood pressure after admission to the hospital. I cannot get much reliable information from the physical examination, and I wonder what this questionable mass was that they thought pulsated in the left side of the abdomen.

Did this man have an aneurysm of the abdominal aorta? From the physical examination described here, I should say that he did not, unless the aneurysm had ruptured, producing a large hematoma in the retroperitoneal tissues. Even if he had that, I think that one would still be able to feel the original abdominal aneurysm. He could have had a slow leak from it and succumbed.

Another possibility is that he had pulmonary embolism. I doubt very much that he died from embolism since he had been walking around until shortly before death. It is most unusual for patients who have been ambulatory to develop a massive fatal pulmonary embolism; they may have minor pulmonary infarcts.

Did he die of coronary heart disease? That is a question which I cannot answer, and I should like someone to interpret the electrocardiograms.

DR. CONGER WILLIAMS: I took both electrocardiograms, so I shall simply say that I found no difference between the two films. I was able to conclude only that the changes were probably of long standing.

DR. LINTON: Are they consistent with coronary heart disease?

DR. WILLIAMS: Consistent with, but not diagnostic of, infarction — that is the way I expressed it.

DR. LINTON: I do not see how we can connect up the heart with the pain in the back and the

abdomen, so far as coronary heart disease or cardiac infarction is concerned. But there is one other condition that ought to be seriously considered. Did he have a dissecting aneurysm of the arch of the aorta? I do not know any positive way of making that diagnosis. If he had had absent pulsations in the arteries to the lower extremities I should more seriously consider such a diagnosis. The patients whom I have seen have had diminution or absence of pulsations in the lower extremities owing to the fact that the blood had dissected down the layers of the aorta and had gradually shut off the arterial flow.

I cannot think of any other possibility that might explain the sudden demise, and I favor the diagnosis of an abdominal aneurysm that had ruptured, with the patient dying as a result.

DR. WILLIAMS: When this patient came in it was obvious that he had some sort of very severe accident, which we thought was vascular. The diagnosis of dissecting aneurysm was considered as time went on. The pulse was almost imperceptible when he came in, but between examinations the pulse gradually increased in strength. The blood pressure nevertheless stayed fairly low, which may have interfered with the pulsation of the mass in the abdomen. As a result of the dilatation in the aorta the cardiac output was very poor. It is interesting that the mass in the abdomen was not visible on the previous evening. The next morning, when we were visiting and stopped outside to discuss the sudden appearance of the mass, the patient died in a period of about thirty seconds.

DR. RICHARDSON: I should like to mention that everything points to the fact that this man had severe hemorrhage. Might it have been within the bowel, an unrecognized ulcer or something else. The mass felt might have been due to a large amount of blood in the bowel that had not been passed. Is that possible?

DR. LINTON: Most patients with massive gastric hemorrhage vomit the blood or pass it by rectum.

DR. RICHARDSON: Most of them do, but I have seen some that did not.

DR. LINTON: Another thing, he vomited but he did not vomit blood. I believe that the vomiting was secondary to vagus stimulation.

DR. RICHARDSON: Owing to blood in the abdominal cavity?

DR. LINTON: Yes; blood in the region of vagal distribution — in the retroperitoneal area.

A PHYSICIAN: How about pain in the back?

DR. LINTON: It seems to fit abdominal aneurysm more than anything else. One might think of acute pancreatitis, but people do not die so suddenly from acute pancreatitis.

DR. RICHARDSON: I was thinking of acute ulcer with hemorrhage.

DR. BENJAMIN CASTLEMAN: A factor against dissecting aneurysm is the fall in blood pressure, which usually remains elevated. With a dissecting aneu-

rysm extending down into the abdominal aorta, dissection almost always extends into the iliac arteries as well and there should be a diminution in the pulse in the legs, as Dr. Linton has intimated.

DR. WILLIAMS: Another point against it is the level of the blood pressure before this happened; it was 160 systolic, 90 diastolic, which is not remarkable. These patients usually have a higher blood pressure, although it has been reported in those with normal blood pressures.

#### CLINICAL DIAGNOSIS

Mesenteric thrombosis?

#### DR. LINTON'S DIAGNOSIS

Ruptured abdominal aortic aneurysm.

#### ANATOMICAL DIAGNOSES

Arteriosclerotic aneurysm of abdominal aorta, with rupture.

Retroperitoneal hematoma, right.

Coronary sclerosis.

Myocardial fibrosis.

Cardiac hypertrophy.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This man had a large arteriosclerotic aneurysm of the aorta beginning below the origin of the renal artery and extending down to the bifurcation. The aneurysm in places had a circumference of 18 cm. It had ruptured on the right side through a large linear tear 8 cm. in length. This tear was undoubtedly the terminal episode; the first attack was probably a small rupture with a slow leak, which accounts for the huge retroperitoneal hematoma that was felt just before he died. The aneurysm was arteriosclerotic, there being no evidence to suggest syphilis. Both common iliac and right hypogastric arteries were also markedly dilated — the diffuse aneurysmal dilatation not infrequently seen with severe arteriosclerosis. The heart was moderately enlarged, weighing 452 gm. There was evidence of severe coronary sclerosis and myocardial fibrosis.

DR. LINTON: I wonder when he had had his most recent clinical checkup. He was supposed to have had them frequently.

DR. WILLIAMS: He was a rather heavy-set man, and it is quite possible his physician would not have been able to feel the aneurysm.

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## PENICILLIN IN BACTERIAL ENDOCARDITIS

Prior to the introduction of the sulfonamides, medical science possessed no effective agent for the treatment of bacterial endocarditis. Sulfonamide therapy constituted a tremendous advance in the management of this disease by demonstrating for the first time that bacterial endocarditis could be cured, but its usefulness proved to be disappointingly limited. The various sulfonamide derivatives had little or no effect on cases of acute bacterial endocarditis, and less than 5 per cent of patients with the subacute form of the disease were permanently benefited by their administration; thus, it soon

became clear that an even more effective chemotherapeutic agent was needed. Surgical treatment, although sometimes successful in patients in whom infection is superimposed on a patent ductus arteriosus, unfortunately offers nothing to the majority of patients with bacterial endocarditis.

Good evidence to the effect that penicillin is a potent agent for the treatment of this disease is beginning to accumulate.<sup>1-3</sup> Further support for this view is to be found in the work of Meads, Harris and Finland, reported elsewhere in this issue of the *Journal*. Of 10 patients with subacute bacterial endocarditis treated with penicillin during 1944, at the Boston City Hospital, 7 had the infection arrested, at least temporarily; and 3 of 7 patients with acute bacterial endocarditis are likewise reported to be well. The results in this relatively small series are in close agreement with those in a much larger group that have been reported to the Committee on Chemotherapeutics and Other Agents of the National Research Council. These reports indicate that, in cases in which the infecting organism was sensitive to the action of the drug, penicillin therapy arrested the infection in 55 to 60 per cent of cases of subacute bacterial endocarditis and in 25 to 40 per cent of cases of acute bacterial endocarditis caused by pyogenic cocci. To accomplish these results, it was necessary to administer not less than 200,000 units of penicillin daily for two or more weeks. When used alone, penicillin was fully as effective as when given in conjunction with an anticoagulant. Thus, the simultaneous administration of heparin or dicumarol appears to be neither necessary nor desirable.

In cases of either subacute or acute bacterial endocarditis in which the infecting organism was shown to be resistant in vitro to the action of penicillin, even extremely large doses of the drug had no effect. It has been recommended, therefore, that before or at the beginning of therapy the causative organism in each case be tested for its susceptibility to penicillin. This procedure is especially indicated in cases of subacute bacterial endocarditis caused by nonhemolytic streptococci. Although most strains of this type of streptococcus are sensitive to penicillin, occasional ones with a high natural resistance to the drug are encountered.<sup>4</sup>

There can be no question that penicillin is the most effective agent now known for the treatment of bacterial endocarditis. It is still too early to estimate in what percentage of cases actual cure of the disease is obtained. Follow-up observations of a year or even longer are needed before the fact of cure can be established. As indicated by the experience at the Boston City Hospital, relapse or reinfection may occur several months after the apparent successful completion of treatment.

Bacterial endocarditis remains a serious disease, and the search for an even more efficient form of therapy will no doubt continue. It is clear, however, that the physician now has at his command an agent that gives promise of curing upward of half the patients suffering from this disease. The early diagnosis of bacterial endocarditis thus becomes a problem of practical importance, as well as one of academic interest.

#### REFERENCES

1. Dawson, M. H., and Hunter, T. H. Treatment of subacute bacterial endocarditis with penicillin; results in twenty cases. *J. A. M. A.* 127:129-137, 1945.
2. Loewe, L. Combined use of penicillin and heparin in treatment of subacute bacterial endocarditis. *Canad. M. A. J.* 52:1-14, 1945.
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4. Dawson, M. H., Hobby, G. L., and Lipman, M. O. Penicillin sensitivity of strains of non-hemolytic streptococci isolated from cases of subacute bacterial endocarditis. *Proc. Soc. Exper. Biol. & Med.* 56:101, 1944.

#### MAY DAY AND BIRTH REGISTRATION

THE first day of May has been set aside as Child Health Day in this country since 1923, a new tradition that was officially sanctioned by Congress in 1928. Its observance is now dignified further through the recognition accorded it by the American Child Health Association, state and provincial health authorities and the Children's Bureau of the United States Department of Labor. In our busy cycle of duties, and of observances and performances, we have fittingly set aside one day each year on which to give thought to the onrushing generations.

It has been customary, in this observance of Child Health Day, to feature some particular point deserving emphasis — the health of young workers in 1943 and immunization against diphtheria and smallpox in 1942. This year, when masses of persons

in other, less fortunate, countries have lost their social security and practically their personal identities, the importance of birth registration has been selected as the May Day feature story.

The significance to everyone of birth registration and the birth certificate is so obvious as hardly to need elaboration. Suffice it to say that it furnishes incontrovertible evidence of one's identity, and on it may depend the right to an education and the right to work, to vote, to marry or to enter civil service. Various other civil rights may hinge on this proof of age and of citizenship — obtaining an automobile license or a pilot's license, Social Security benefits and the settlement of pensions. On this evidence of birth may also depend the proof of parentage and of legal dependency, the inheritance of property and the settlement of insurance.

The registration of births is an obligation that falls almost entirely on the attendant at the birth, which, in this state, ordinarily means the physician. Massachusetts stands well in its record of birth registrations, ranking, with its total percentage of 98.9, high among the twenty-eight states and the District of Columbia with registrations of 95 per cent and over. In this it is surpassed, in fact, only by Connecticut, New Jersey and Minnesota. Among the less adequately registered southern states, Arkansas trails, with a percentage of 75.9.

A registration percentage of 98.9 is good, although it can and should be better. When we realize that, in the Nation, since the attack on Pearl Harbor about 700,000 babies have been born who are still unregistered, we become aware of a figure that we can face less complacently.

#### MASSACHUSETTS MEDICAL SOCIETY

##### TREASURER'S REPORT COVERING DISTRIBUTION OF REFUND

The Treasurer of the Massachusetts Medical Society makes the following report regarding the refund to district societies for 1944:

The Council voted to distribute the sum of \$4000 to district societies. The total number of payments of annual dues received by the Treasurer by March 1, to be counted for the refund, was 3297. The refund to the district societies for each paid fellow is therefore \$1.213.

The following table gives the number of payments, as of March 1, and the refund to each district as of April 3:

DISTRICT	NUMBER REPORTED PAID	REFUND
Barnstable	32	\$38 87
Berkshire	88	106 78
Bristol North	45	54 63
Bristol South	139	168 64
Essex North	128	155.30
Essex South	191	231.72
Franklin	31	37 65
Hampden	210	254 76
Hampshire	49	59 48
Middlesex East	83	100 74
Middlesex North	80	97 08
Middlesex South	661	801.83
Norfolk	587	712 06
Norfolk South	93	112.86
Plymouth	98	118.92
Suffolk	442	536 18
Worcester	275	333 61
Worcester North	65	78 89
	- 3297	\$4000 00

In 1944, for comparison, the total number of payments for the refund was 3060.

ELIOT HUBBARD, JR., M.D., *Treasurer*

DEATH

KNOWLTON — Charles D. Knowlton, M.D., of Rockport, died January 5. He was in his seventy-eighth year.  
Dr. Knowlton received his degree from Tufts College Medical School in 1894. He later studied at the University of Pennsylvania School of Medicine and at the University of Berlin. He was formerly assistant professor of theory and practice of medicine at Tufts College Medical School and instructor in laryngology at Harvard Medical School. He was a consulting surgeon at the Massachusetts Eye and Ear Infirmary and was formerly president of the Norfolk District Medical Society. He was an affiliate fellow of the American Medical Association.

NEW HAMPSHIRE  
MEDICAL SOCIETY

DEATH

FLANDERS — Louis W. Flanders, M.D., of Dover, died January 16. He was in his eighty-first year.  
Dr. Flanders received his degree from the University of Vermont College of Medicine in 1885. He was a member of the Strafford County Medical Society and the New Hampshire Medical Society. He was a past president of the New Hampshire Medical Society.  
His widow, a son, two sisters and a brother survive.

WESTON — Arthur F. Weston, of Keene, died March 25. He was in his seventy-third year.  
Dr. Weston received his degree from Boston University School of Medicine in 1903.  
His widow, a daughter and a sister survive.

MISCELLANY

ANNUAL PRIZE SUBSCRIPTION

The annual prize subscription offered by the *New England Journal of Medicine* for the best undergraduate contribution to the *Tufts Medical Journal* has been awarded to A. Harvey Salans, '46, for his paper "Rheumatic Fever: A major public-health problem," which appeared in the June, 1944, issue. The paper "Penicillin: A review," by Henry H. Banks, '46, received honorable mention; it appeared in the April, 1944, issue. According to custom, these students will be given a two-year and a one-year subscription to the *Journal*, respectively.

CORRESPONDENCE

SCHOOL PHYSICIANS

To the Editor: When any medical journal prints an editorial in which the school physician is even mentioned, that event becomes front-page news.

The editorial in the March 15 issue of the *Journal*, concerning the Strayer survey, had some pertinent things to say about school health programs in general. Every experienced school physician will agree with the statement that health service "suffers from overdetalled legal prescriptions and inferior physical equipment." One of the reasons, perhaps the greatest one, for this situation is the attitude of organized medicine. The position of school physician is a legitimate specialty in medicine, but it has never been recognized as such by the Massachusetts Medical Society. The school physician is the only member of the school staff whose basic training qualifies him to head up the school health program. If organized medicine fails to give public recognition and professional support to this work, how can we expect city and town officials to provide adequate financial support for it?

WHITMAN G. STICKNEY, M.D.

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Beverly, Massachusetts

DIAGNOSTIC TEST DOSE OF NEOSTIGMINE

On page 289 of the March 8 issue of the *Journal* mention is made, in the discussion of one of the case records of the Massachusetts General Hospital, of the neostigmine (Prostigmin) test for myasthenia gravis. The dose used for this test is given as 0.5 mg. of neostigmine methylsulfate by intramuscular injection. This is not sufficient when the drug is to be used as a diagnostic test in an adult. The matter of dosage was pointed out by Schwab and myself (Schwab, R. S., and Viets, H. R. Prostigmin test in myasthenia gravis. *New Eng. J. Med.* 219:226-228, 1938), 1.5 mg. of neostigmine methylsulfate being advised. Since that time, a special diagnostic ampule has been put on the market; this contains 1.5 mg. of neostigmine methylsulfate and 0.6 mg. of atropine sulfate. In order to avoid a false, negative or incomplete report, the dosage contained in the diagnostic ampule is recommended.

HENRY R. VIETS, M.D.

Myasthenia Gravis Clinic  
Massachusetts General Hospital  
Boston 14

A PLEA FOR MIDDLESEX

To the Editor: The editorial "Standards of Medical Education" in the February 1 issue of the *Journal* was quite interesting. I, too, am one of those whose photograph is represented by the historic picture taken when Governor James M. Curley signed that bill. Let us be fair and reasonable. So long as the Commonwealth of Massachusetts has chartered a medical school and recognized the graduates, is it logical to recognize graduates from other states when those states refuse to recognize all graduates from Massachusetts? There are several states which refuse to recognize graduates from other states because the latter discriminate by failing to give recognition to graduates of the former, for example, Ohio, New York and Connecticut. Why does not Massachusetts protect its own graduates?

There are a few hundred graduates from Middlesex University School of Medicine who are fellows of the Medical Society; there are many commissioned officers in the armed forces from Middlesex; there is a graduate from Middlesex who is medical examiner appointed by former Governor Saltonstall; a graduate from Middlesex was appointed to the United States Public Health Service; there is a health officer in one of the neighboring cities of Boston who is a Middlesex graduate; many Middlesex graduates completed their internships in some of the finest hospitals; many Middlesex graduates are in active practice; several Middlesex graduates are on the staffs in a few hospitals in the Commonwealth; and there are several Middlesex graduates practicing in other states. Yet, in spite of all this, graduates from Middlesex are discriminated against in hospitals, in appointments and even at the present time in the armed forces. When they entered on the study of medicine, they had all the necessary requirements; they completed the prescribed courses, as per law; they received their M.D. degrees; they underwent their required internships; and they passed the medical licensing examinations. Still, they are not given the

same opportunity as other graduates. It is a shame to penalize such qualified graduates.

Middlesex is showing that she is willing to do everything that is humanly possible to improve the medical school in order to get recognition. Why does not the Massachusetts Medical Society, which is playing such a vital part, and the Approving Authority and the American Medical Association do everything possible to help Middlesex? I can name medical schools which were not given full recognition by the New York State Board of Regents but which, with the proper help, did receive recognition. Unless complete co-operation is shown to help Middlesex become as good a medical school as any other, I firmly feel that the General Court should pass legislation to eliminate the Approving Authority and should also pass laws forbidding recognition to graduates from other states that refuse to recognize all graduates from our medical schools. If full recognition in all hospitals were given to its graduates, other states would follow suit.

BERNARD ZUCKERMAN, M.D.

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## NOTICES

### BOSTON DISPENSARY

A clinical staff meeting of the Boston Dispensary will be held at the Pratt Hospital Auditorium on Friday, May 4, at 12:30 p.m. Dr. Daniel L. Lynch will speak on the subject "Rehabilitation Problems in Industry." Luncheon will be served at 12 noon.

### SUFFOLK DISTRICT MEDICAL SOCIETY

A dinner meeting of the Suffolk District Medical Society will take place on Saturday, April 28, at 7 p.m., at the Harvard Club of Boston. Surgeon-General Thomas Parran, of the United States Public Health Service, will speak on the subject "Place of the Hospital in Postwar Medical Care." Tickets \$3.75.

### TUFTS ALPHA OMEGA ALPHA

The Tufts chapter of the Alpha Omega Alpha will meet in the Auditorium of the Beth Israel Hospital, Boston, on Wednesday, May 9, at 8:15 p.m. Dr. Fuller Albright will speak on the subject "Action of Vitamin D."

### JOSEPH H. PRATT

#### DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a.m.

#### MEDICAL CONFERENCE PROGRAM

Wednesday, May 2 — The Spleen, the Bone Marrow, and Thrombopenic Purpura. Dr. William Dameshek.

Friday, May 4 — The Heart in Hypertension since the Days of Richard Bright. Dr. Paul D. White.

Wednesday, May 9 — Cardiac Clinic. Dr. Heinz Magendanz.

Friday, May 11 — Carcinoma of the Prostate. Dr. William C. Quimby.

Tuesday, May 15 — Clinicopathological conference. Drs. Chester S. Keefer and H. E. MacMahon.

Wednesday, May 16 — Endocrine Problems in Childhood. Dr. Richard Wagner.

Friday, May 18 — Thyroid Disease. Dr. Frank H. Lahey.

Wednesday, May 23 — Common Duct Stone: A review of cases. Dr. William T. Roberts.

Friday, May 25 — Peri-Arteritis Nodosa and Acute Disseminated Lupus from the X-ray Viewpoint. Dr. Merrill Sosman.

On Monday mornings (except May 7) clinics will be given by Dr. Samuel Proger. On Tuesday and Thursday mornings Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings clinics will be given by Dr. William Dameshek.

## NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, May 3, in the classroom of the nurses' residence.

### PROGRAM

Laryngotracheobronchitis: Brief summary of six cases having penicillin treatment. Drs. Helen N. Perry and Clara Waldinger.

Bacteriological Observations and Local Use of Penicillin. Miss Anita B. Mangiaracine.

Discussion of nasal drops.

Dr. Margaret Noyes Kleinert will be chairman.

## EDWARD K. DUNHAM LECTURES

The Faculty of Medicine of Harvard University has announced that the following lectures on the general topic "The Insect as a Medium for the Study of Physiology" will be delivered by Dr. Vincent B. Wigglesworth under the Edward K. Dunham Lectureship for the Promotion of the Medical Sciences:

Monday, May 7. The Insect Cuticle as a Living System.

Wednesday, May 9. Hormones and the Regulation of Insect Growth.

Friday, May 11. Integration in the Epidermis of Insects.

These lectures are scheduled for 5 p.m. at the Harvard Medical School, Building C Amphitheater.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 3

#### FRIDAY, MAY 4

\*9:00-10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Mallory Building, Boston City Hospital.

#### SATURDAY, MAY 5

\*10:00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

#### MONDAY, MAY 7

\*12:00 m.-1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

#### TUESDAY, MAY 8

\*9:00-10:00 a.m. Medical clinic. Infants' Hospital.

\*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

#### WEDNESDAY, MAY 9

\*12:00 m. Clinicopathological conference. Children's Hospital.

\*12:00 m.-1:00 p.m. Clinicopathological conference, Cambridge Hospital.

\*Open to the medical profession

APRIL 28. Suffolk District Medical Society. Notice elsewhere on this page.  
APRIL 30. New York Institute of Clinical Oral Pathology. Page 334, issue of March 15.

MAY 2-25. Joseph H. Pratt Diagnostic Hospital. Medical conference program. Notice elsewhere on this page.

MAY 3. New England Hospital for Women and Children. Notice elsewhere on this page.

MAY 4. Boston Dispensary. Notice elsewhere on this page.

MAY 7, 9 and 11. Edward K. Dunham Lectures. Notice elsewhere on this page.

MAY 9. Tufts Alpha Omega Alpha. Notice elsewhere on this page.

MAY 10. Advances in Obstetric Technics. Dr. Roy J. Heffernan. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

JUNE 14-19. American Board of Obstetrics and Gynecology. Page 364, issue of March 22.

SEPTEMBER 17. American Public Health Association. Page 752, issue of November 30.

## DISTRICT MEDICAL SOCIETIES

### PLYMOUTH

MAY 17. Lakeville Sanatorium, Lakeville. 11 a.m.

### WORCESTER

MAY 9. Annual meeting.

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## THE CARDINAL MANIFESTATIONS OF PAROXYSMAL TACHYCARDIA\*

### I. Anginal Pain

LOUIS WOLFF, M.D.†

BOSTON

THE symptoms accompanying paroxysmal tachycardia are numerous and varied. Most of them are not caused directly by the tachycardia, nor are they directly or specifically related to the underlying heart condition. Inquiry into the circumstances under which they arise throws no light on their meaning or on the underlying cardiovascular status. A few of the symptoms, however, arise under such constant conditions that they create a uniform clinical pattern. Because these symptoms—palpitation, pulmonary congestion, anginal pain, congestive failure, vascular collapse, central-nervous-system manifestations and embolism—may be correlated with significant variables, such as the type of patient, the heart lesion, the functional status of the heart and circulation, the ventricular rate and the presence or absence of embolism, it is proper to designate them as the cardinal manifestations of paroxysmal tachycardia. A detailed clinical analysis of 125 cases served as the basis for these and other conclusions, which were reported in a previous publication.<sup>1</sup> The present series of papers is devoted to a consideration, in greater detail, of some of the cardinal manifestations previously discussed. To the first group of 125 cases have been added 128 unselected new ones, making a total of 253. All cases had an electrocardiogram, confirming the presence of an abnormal rhythm and providing the ventricular rate during the paroxysm.

#### NONANGINAL CHEST PAIN

Chest pain is usually mentioned as one of the symptoms associated with paroxysmal tachycardia, but its incidence, character and significance are variously estimated or entirely disregarded by different authors. In 1888, in a paper containing the first clear description of paroxysmal tachycardia, Bristowe<sup>2</sup> stated that 1 of his 9 patients had anginal-like attacks during the paroxysms of rapid heart

action; similar observations have been reported by other authors<sup>3-6</sup> in single case reports. Barnes and Willis<sup>7</sup> noted the occurrence of anginal pain in 19 of 380 cases of paroxysmal tachycardia; the pain was usually described as a precordial ache; in no case did angina pectoris occur between the paroxysms. In 4 cases reported by White and Camp<sup>8</sup> and in some of those previously reported by me<sup>1, 9</sup> there was angina pectoris on effort; the former authors considered the induction of anginal pain by paroxysmal tachycardia a rare disorder. Campbell and Elliott<sup>10</sup> stated that tightness in the chest was present in most attacks of paroxysmal tachycardia and was of no special significance; in 12 of their 100 cases there was anginal pain, which was considered benign because induced by paroxysmal tachycardia. Williams and Ellis<sup>11</sup> recorded the occurrence of severe substernal pain in 2 patients during paroxysmal ventricular tachycardia; both patients had large hearts but were free of angina pectoris between paroxysms. The first study in which the induction of anginal pain by paroxysmal tachycardia was correlated with specific cardiovascular conditions was reported from this clinic in the paper referred to above.<sup>1</sup>

Analysis of the present larger series of cases shows that anginal pain was present during paroxysms of tachycardia in 40 cases, or 16 per cent of the series; these will be discussed in detail below. An almost equal number of patients had pain that was not anginal in character. In view of the significance of anginal pain in paroxysmal tachycardia, it is necessary to make a clear distinction between it and other types of pain. Nonanginal pain is frequently described as a precordial ache or distress, during or following the cessation of paroxysms of tachycardia. This is particularly frequent in patients with mitral stenosis, but is not limited to this group. Other patients are conscious of a tired or weak feeling in the region of the heart. Occasionally the cause of pain is the palpitation itself. This painful palpitation is usually seen in sensitive persons; consciousness of the heart action is interpreted by them as pain and is extremely disturbing; as the

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paroxysm ends there may be a severe, sharp, momentary exacerbation of the pain. Another type of non-anginal pain associated with tachycardia is sharp, pleuritic-like pain, often of great severity, over the precordium and left shoulder, occurring with inspiration. Upper abdominal pain due to acute congestion of the liver from an exacerbation of congestive failure secondary to paroxysmal rapid heart action may suggest anginal pain but should be differentiated without difficulty. Some patients complain of momentary twinges of precordial pain during paroxysms of tachycardia, and as a rule, similar pains are experienced between paroxysms; in other patients, vague, unexplained chest pain is noted during tachycardia. There is little to suggest anginal pain in these cases. In patients with neurocirculatory asthenia, pain is frequent with paroxysms of tachycardia, as it is during the normal cardiac mechanism. Another type of pain is so-called "imitation angina," occurring in those familiar with the syndrome of angina pectoris, such as physicians or nurses.

The remaining examples of nonanginal pain associated with paroxysmal tachycardia have no relation to heart disease or are not at all related to the tachycardia. The most important of these are pulmonary embolism and pericarditis.<sup>12</sup> In this series other causes of pain simulating angina pectoris and associated with paroxysmal tachycardia were peptic ulcer, gall-bladder disease, chest trauma or fractured ribs, neoplastic disease in the chest, post-operative pain in the upper abdomen or lower chest, splenic infarct and spontaneous pneumothorax. Pain, at times simulating angina pectoris, may occur in all these conditions, which may be complicated by paroxysmal tachycardia; the pain is due to the underlying condition and not to the tachycardia.

CASE 1. S. S., a 25-year-old man, had painless paroxysmal auricular fibrillation, but careful study revealed no evidence of organic heart disease. After exercising in a gymnasium, he was seized with severe, constricting precordial pain. An electrocardiogram showed auricular fibrillation with a ventricular rate of 120. Investigation revealed that the pain was due to spontaneous pneumothorax.

#### ANGINAL PAIN

Pain with the features characteristic of angina pectoris was classified as anginal pain regardless of duration. Since the pain in these cases was induced by tachycardia, the ordinary inciting causes of effort and emotion were absent. Most of these patients also had angina pectoris with effort or emotion; the similarity of the pain induced by paroxysmal tachycardia to that occurring at other times facilitated its interpretation. The duration of the pain depended on the duration of the tachycardia and the coincidental occurrence of acute myocardial infarction. With very short paroxysms the pain was identical with an ordinary attack of angina pectoris, but with prolonged tachycardia the pain was intermittent (status anginosus) or continuous, simulating acute myocardial infarction. The latter term

is used in its widely accepted clinical sense, but includes major coronary attacks with evidence of heart-tissue necrosis. A diagnosis of acute myocardial infarction was made in 10 of the 40 cases having anginal pain.

#### *Pain in the Absence of Acute Myocardial Infarction*

Anginal pain in the absence of myocardial infarction was induced by paroxysmal tachycardia in 30 cases. The ages of the patients in this group ranged from twenty-eight to eighty-five years; there were 5 cases in the fifth decade, 9 each in the sixth and seventh, 5 in the eighth and 1 in the ninth. The single 28-year-old patient had rheumatic heart disease and free aortic insufficiency. There were 15 cases of paroxysmal auricular fibrillation (50 per cent), 9 of paroxysmal auricular tachycardia (30 per cent), 4 of paroxysmal auricular flutter (13 per cent) and 2 of paroxysmal ventricular tachycardia (7 per cent). The ventricular rate was 150 per minute or more in 26 cases, 140 in 3 and 120 in 1. Twenty-two patients gave a clear history of angina pectoris on effort, but no such history could be elicited in the remaining 8 cases. Of the latter, 3 developed acute myocardial infarction one to seven days after paroxysmal tachycardia had induced anginal pain. One patient had free aortic insufficiency; another had had an acute myocardial infarct six years previously, but no angina pectoris for a year preceding the induction of anginal pain by paroxysmal ventricular tachycardia. One patient in this group was a seventy-five-year-old woman with hypertensive heart disease and crippling arthritis. Only 2 patients had apparently normal hearts. Thus, of the 30 patients in whom paroxysmal tachycardia induced anginal pain, 73 per cent had exertional angina, 10 per cent did not have angina pectoris but developed acute myocardial infarction within a few days after paroxysmal tachycardia-induced anginal pain, 10 per cent had organic heart disease, and 7 per cent had normal hearts.

The following 4 cases are typical examples of the induction of anginal pain by paroxysmal tachycardia.

CASE 2. I. O., a 65-year-old man, had had angina pectoris on effort for 3 or 4 years, always relieved by nitroglycerin. While in the hospital he had repeated attacks at rest, always associated with paroxysmal auricular tachycardia with a ventricular rate of 170. The pain lasted continuously during the tachycardia and was not relieved by nitroglycerin, but ended at once when the abnormal rhythm was terminated.

CASE 3. S. W., a 58-year-old man, had a history of old myocardial infarction, paroxysmal dyspnea and angina pectoris on effort. During a routine examination he had repeated attacks of angina pectoris, weakness and faintness. It was noted that the episodes of pain coincided with extremely rapid heart action, and that when the heart rate suddenly slowed spontaneously or as the result of gentle stimulation of the right carotid sinus, the pain immediately disappeared. An electrocardiogram showed paroxysmal auricular tachycardia with an auricular rate of 214 and intermittent 2:1 auriculoventricular block, with a resulting ventricular rate of either 214 or 107.

CASE 4. S. G., a 66-year-old woman, had had paroxysmal tachycardia for 50 years, associated with vascular collapse. Ever since the menopause 15 years previously, she had had hot flashes and the attacks of paroxysmal rapid heart action had increased in frequency. For several years effort provoked substernal, squeezing pain radiating into the back. Similar pain was induced during the same period by the paroxysms of tachycardia. When seen during an attack of pain the patient was in collapse: with a pale, moist skin, absent radial pulsations and a blood pressure of 76/70. The clinical picture was that of acute myocardial infarction. The heart rate, however, was very rapid, and an electrocardiogram showed paroxysmal auricular tachycardia with a ventricular rate of 200. Stimulation of the right carotid sinus interrupted the abnormal rhythm, with immediate cessation of the pain and return of a normal pulse and blood pressure. The patient was seen in several similar attacks, and at no time was evidence of myocardial infarction obtained. She died suddenly some months later.

CASE 5. M. T., a 62-year-old male with a negative cardiovascular history, had a partial gastrectomy for a penetrating ulcer of the stomach. During convalescence he had a paroxysm of auricular flutter with a ventricular rate of 170; no symptoms were provoked, and he was entirely unaware of the paroxysm. Within 24 hours a second paroxysm with a ventricular rate of 166 occurred, but that time it induced anginal pain; when the paroxysm ended, the pain disappeared. On the following day, he developed severe, prolonged anginal pain, although the heart rhythm was normal. This was followed by elevation of the temperature and white-cell count and serial electrocardiographic changes indicating the presence of acute myocardial infarction.

#### *Pain Associated with Acute Myocardial Infarction*

The ages of the 10 patients in this group ranged from fifty-five to eighty-five; there were 2 cases in the sixth decade, 5 in the seventh, 2 in the eighth and 1 in the ninth. There were 4 cases of paroxysmal auricular fibrillation, 3 of paroxysmal auricular tachycardia, 2 of paroxysmal ventricular tachycardia and 1 of paroxysmal auricular flutter. The ventricular rate was 150 per minute in 5 cases and 154, 166, 170, 180 and 200, respectively, in the others. The onset of the arrhythmia and acute myocardial infarction appeared to be simultaneous in 4 cases; the tachycardia in 2 of these ended spontaneously after some hours, but the pain persisted, whereas in another the pain disappeared several hours after the attack began despite the continuance of paroxysmal auricular tachycardia for another twenty-four hours. Paroxysmal ventricular tachycardia with a ventricular rate of 170 occurred in 1 case on the third day of acute myocardial infarction, but did not appear to increase the pain, which was still present; two weeks later, after there had been no pain for over a week, paroxysmal ventricular tachycardia, with a ventricular rate of 170 to 180 recurred, but did not induce pain. Paroxysmal tachycardia in 3 cases occurred on the second to fourth days of acute infarction, while pain was still present but apparently without influencing it. On the sixth day after the onset of acute infarction in another case, intermittent anginal pain was still occurring, and was also induced by a paroxysm of auricular tachycardia with a ventricular rate of 150. The tenth patient continued to have spontaneous angina pectoris for

four weeks following acute myocardial infarction, and paroxysmal ventricular tachycardia on the tenth and twenty-fifth days, respectively, induced anginal pain.

CASE 6. J. H., a 70-year-old woman, had a history of diabetes, hypertensive heart disease and a previous cerebral accident. Her first attack of precordial oppression, accompanied by palpitation, a rapid heart rate and dyspnea, necessitated a hypodermic injection of morphine sulfate. On the following day the symptoms were still present and she was admitted to the hospital, where an electrocardiogram showed paroxysmal auricular tachycardia with a ventricular rate of 166. Three hours after the subcutaneous injection of morphine sulfate the pain disappeared, but the paroxysmal auricular tachycardia, without any change in rate, continued for another 24 hours. The data clearly indicated the presence of acute myocardial infarction.

CASE 7. S. A., a 75-year-old woman with an apparently normal heart, had had for 5 years prolonged attacks of paroxysmal auricular tachycardia in which the only symptom was palpitation. She then had an attack of pressure in the chest, quickly went into shock and developed pulmonary edema. Examination showed paroxysmal auricular tachycardia with a ventricular rate of 200. The tachycardia stopped after 4 hours, but pain and shock continued for 4 to 5 days. The electrocardiographic and other evidence indicated the presence of acute myocardial infarction. Following recovery she had angina pectoris, both on effort and with paroxysmal auricular tachycardia.

#### FAILURE OF PAROXYSMAL TACHYCARDIA TO INDUCE ANGINAL PAIN IN CORONARY HEART DISEASE

Paroxysmal tachycardia failed to induce anginal pain in 48 cases of coronary heart disease. All the patients in this group had a past or present history of angina pectoris or myocardial infarction or post-mortem evidence of significant coronary-artery disease. There was 1 patient in the fourth decade, three in the fifth, 12 in the sixth, 17 in the seventh, fourteen in the eighth and 1 in the ninth. Twenty-four (50 per cent) had paroxysmal auricular fibrillation, 12 (25 per cent) paroxysmal ventricular tachycardia, 9 (19 per cent) paroxysmal auricular flutter and 3 (6 per cent) paroxysmal auricular tachycardia. The ventricular rate was 150 or more in 32 cases and less than 150 in 16 cases.

#### *Ventricular Rate Less Than 150*

Of the 16 cases in this group, paroxysmal tachycardia complicated acute or recent myocardial infarction in 9. Paroxysmal auricular fibrillation with a ventricular rate of 120 per minute failed to induce anginal pain in a patient who was still having intermittent pain following a recent infarct. In 5 patients with a past history of angina pectoris on effort, paroxysmal tachycardia on the sixth, fourth, tenth, fourteenth and fifth days, respectively, following the onset of acute myocardial infarction failed to induce anginal pain, nor was pain occurring otherwise in these patients. The 3 remaining patients with acute infarction were asymptomatic (without pain) when paroxysmal tachycardia on the third, fourth and seventh days, respectively, failed to induce anginal pain.

Three patients with angina pectoris on effort had no pain during tachycardia with ventricular rates less than 150. The remaining 4 patients did not have exertional angina and pain was not induced by tachycardia; 2 had a previous history of myocardial infarction, and in the other 2 post-mortem examination disclosed the presence of significant coronary disease.

#### *Ventricular Rate 150 or More*

Thirty-two patients with coronary heart disease did not have anginal pain during paroxysmal tachycardia with a ventricular rate of 150 or more. Acute or recent myocardial infarction was present in 18 cases, in each one of which the tachycardia occurred when the illness had become painless. The tachycardia occurred on the following days after the onset of acute infarction: in 1 case on the third day, in 3 on the fifth, in 1 on the sixth, in 1 on the eighth, in 4 on the tenth, in 1 at the end of two weeks, in 2 at the end of three weeks and in the remaining 5 after five to eight weeks. Seven patients had had angina on effort for variable lengths of time preceding the onset of acute infarction.

There remain in this group 14 patients in whom paroxysmal tachycardia with ventricular rates of 150 or more did not induce anginal pain. Only 3 of these patients had a history of effort angina, which, however, had disappeared many months before the onset of paroxysmal tachycardia; post-mortem examination disclosed significant coronary disease in 2 of these. Five patients had a history of old myocardial infarction but not of angina pectoris, and autopsy confirmed the diagnosis in the 1 patient who died. In the remaining 6 cases, angina pectoris or myocardial infarction had never been observed during life, but at autopsy significant coronary disease was found in all of them.

#### DISCUSSION

The present study of anginal pain in relation to paroxysmal rapid heart action has confirmed many of the conclusions stated in the previous report<sup>1</sup> and has revealed other facts of practical interest. The critical ventricular rate for the induction of anginal pain is about 150; pain is not provoked below this level. Paroxysmal tachycardia invariably induces anginal pain in patients with angina on effort, provided the ventricular rate is 150 or more; the ventricular rate, not the type of rhythm, is the significant factor. With few exceptions, patients in whom tachycardia induces anginal pain have organic heart disease, mostly coronary heart disease and angina pectoris and occasionally aortic valvular disease; such patients rarely have normal hearts. When anginal pain is induced by paroxysmal tachycardia in patients who do not have effort angina, it suggests acute myocardial infarction, or it may be a premonitory symptom of infarction. It may also indicate disease of an entirely different

nature, such as pulmonary embolism or pericarditis, in which the tachycardia bears no relation to the pain but is merely a complication of the underlying disease, which itself is responsible for the pain. These and other possibilities must be considered particularly when pain is present during tachycardia with rates well under 150 or when pain is associated with tachycardia for the first time with a history of preceding painless paroxysms. When the ventricular rate is less than 150, pain is generally not due to the tachycardia.

Pain was present in only 10 of the 37 cases of acute or recent myocardial infarction in this series. Of greater significance than the ventricular rate in these cases is the time of occurrence of the tachycardia in relation to the onset of infarction, or, more precisely, the fact that pain of infarction or intermittent, spontaneous anginal pain is or is not still occurring when the tachycardia begins. When tachycardia occurs early in the course of infarction, while continuous pain is present, it may or may not enhance the pain, which may even disappear while the tachycardia continues; but if, following infarction, spontaneous intermittent pain is occurring, the tachycardia invariably induces anginal pain, provided the ventricular rate is 150 or more. Once the constant or intermittent pain associated with infarction has disappeared, paroxysmal tachycardia, regardless of the ventricular rate, does not induce anginal pain.

In cases of asymptomatic coronary heart disease, paroxysmal tachycardia does not induce anginal pain. This group comprises those who never had angina on effort, those with a past history of myocardial infarction or angina pectoris and those with acute and recent myocardial infarction in the painless stage. It is obvious that failure of paroxysmal tachycardia to induce anginal pain does not exclude the presence of coronary heart disease.

#### SUMMARY

The clinical data of 253 cases of paroxysmal tachycardia are analyzed with reference to the occurrence of chest pain.

Chest pain, anginal and otherwise, is a frequent symptom in association with paroxysmal tachycardia. Anginal pain occurs under constant conditions and is therefore one of the cardinal manifestations of paroxysmal tachycardia. It occurred in 16 per cent of the cases in this series.

Anginal pain is invariably provoked by paroxysms of rapid heart action in patients with angina pectoris, provided the ventricular rate is 150 (the critical level) or more.

In the great majority of cases in which paroxysmal tachycardia induces anginal pain, coronary heart disease, usually with angina pectoris, is present.

The association of anginal pain and paroxysmal tachycardia, with ventricular rates under 150 or regardless of the rate, in patients without a history of

angina pectoris suggests various diagnostic possibilities, both cardiac and noncardiac.

Paroxysmal tachycardia does not always enhance the pain of acute myocardial infarction.

The failure of paroxysmal tachycardia to induce pain does not exclude the presence of coronary heart disease, acute, recent or old myocardial infarction or angina pectoris in the past.

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## A MODIFICATION OF AN OLD AND SIMPLE METHOD OF TREATING RECTAL PROLAPSE\*

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UNFAMILIAR at the time with the literature on rectal prolapse, yet with a distinct impression that the various treatments employed were not consistently satisfactory, I tried in October, 1939, a method that I humorously named the "garden-hose" technic. I had a feeling of originality that I soon learned was only partially justified. As will become apparent, this method may hardly be classified under the heading of the art of surgery, but the results thus far, in view of the simplicity of the procedure, have been fairly good.

CASE 1. M. C., a 71-year-old, married woman, had a 12.5-cm. procidentia of the rectum. A section of ordinary garden hose 15 cm. long, with an external diameter of approximately 2.5 cm. and an internal diameter of about 1.8 cm., was chosen because of its noncompressibility. In it a circular groove 1.5 cm. wide was cut deeply 4.0 cm. from the end to be inserted into the bowel. The patient was narcotized with morphine and scopolamine. The rectal sleeve was dragged out its full length and carefully palpated for the presence of small intestine in the herniated pouch of Douglas. With the aid of lubricating jelly, the hose was inserted so that its groove came just distal to the anal margin. Compression of the bowel against the groove was accomplished by ligatures of doubled No. 2 chromic catgut and strong, narrow rubber bands. As a further precaution against too early expulsion of the hose, the end of the prolapse was clamped to its outer end. The operation was performed in 13 minutes.

The postoperative course was reasonably comfortable, although the patient was alarmingly febrile. On the 13th day, the hose and slough came away. She was discharged on the 23rd day. There have been no rectal complaints, and repeated examinations have revealed no abnormalities during the 4 years and 11 months that have elapsed.

CASE 2. S. T., a 67-year-old, married woman, had a 5-cm. prolapse. In November, 1940, an operation similar to that described in Case 1 was done, with short anesthesia by ether. Convalescence was short and uneventful. The hose was removed on the 6th postoperative day and the patient was discharged on the 12th day. After 1 year there was a recurrence

4 cm. long, and in September, 1942, the same operation was performed, along with a small plastic for exertional urinary incontinence, but at that time constriction was made by twisting copper wire of 1.5-mm. diameter around the mass with electrician's pliers. Succinylsulfathiazole was given preoperatively and postoperatively, and ether was the anesthetic. Convalescence was uneventful. The hose was expelled on the 11th postoperative day and the patient was discharged on the 15th day. She remained cured for 1 year and 6 months. Symptoms recurred in March, 1944, and there is now a recurrence that starts 3 cm. above the anus and protrudes for 3 cm. on straining. Eighteen centimeters of bowel has already been removed, and 12 cm. more soon will be. Perhaps one of the newer procedures by the abdominal route would be more effective,<sup>1,2</sup> but in view of the patient's age the risk of another recurrence in 1 or 2 years is preferable.

CASE 3. A. M. P., a 64-year-old, unmarried woman, had a 6-cm. prolapse of the rectum. In May, 1941, an operation similar to that in Case 1 was performed, with anesthesia by ether. Convalescence was uneventful, and the patient was discharged on the 19th postoperative day. A stenosis formed that required repeated dilatation during the following 4 months and has for the last 3 years given occasional slight trouble. The patient is satisfied with the result, and there has been no recurrence of prolapse.

CASE 4. E. C., a 69-year-old, married woman, had an 8-cm. procidentia of the rectum. She received succinylsulfathiazole preoperatively and postoperatively. In September, 1942, under short anesthesia by Pentothal Sodium, the same technic as that described above was employed, compression being accomplished by wire and pliers. The postoperative course was smooth. On the 11th day most remaining slough was removed by cutting against the hose, which was then withdrawn. The patient was discharged on the 15th day. During the last 2 years she has not admitted a complaint, but she has had a stricture 4 cm. above the anus. This was twice dilated in the fall of 1943. It now has a lumen 1.7 cm. in diameter.

CASE 5. M. J., a 51-year-old, married woman, had a 9-cm. procidentia of the rectum, 7 cm. in diameter. Disturbed by the strictures in the previous 2 patients, even though they were of minor inconvenience, I reasoned that they had occurred because of too short a diameter of the hose at the groove of compression. Therefore, instead of cutting a groove, I built up a circular trough as follows. First, the external diameter of the hose was increased to 3 cm. by winding broad adhesive plaster around it. On each side 4 cm. from the end to be inserted into the rectum 2-cm. adhesive

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plaster was wound, leaving a trough 1.5 cm. wide and 0.5 cm. deep.

The patient received succinylsulfathiazole preoperatively and postoperatively. A plastic operation for a lacerated perineum and a large rectocele with enterocele was performed in December, 1942, ether being the anesthetic, before proceeding with the "garden-hose" maneuver. Constriction was made with copper wire, the ends of which were left long and hooked into the outer lumen of the hose. On the 6th postoperative day most of the slough was cut away. Fecal obstruction of the large intestine was easily cleared by enemas given through the hose, which was removed on the 8th day. Convalescence was excellent, and the patient was discharged on the 14th day. She has been well for 1 year and 9 months, and there has been no narrowing of the rectal lumen or recurrent prolapse.

Four of these patients were elderly and frail and had cardiovascular disease; the fifth was obese. Until two years ago, catharsis and enemas were given as part of the preoperative preparation and defecation was inhibited by tincture of opium for ten days postoperatively. Succinylsulfathiazole has made this regime unnecessary and has apparently been the chief factor in achieving practically afebrile convalescences. The daily use of soap and water, boric acid powder and dry dressings was adequate for the care of the local area. All the patients had stretched, relaxed anal sphincters before treatment, and in all cases good muscular tone returned afterward. If one is not sure that the herniated pouch of Douglas is empty, there is no stringent contraindication to incising the anterior side of the rectal procidentia well below the anal margin and exploring before proceeding with constriction. I have not yet considered it necessary to do this.

### DISCUSSION

Older methods of achieving constriction amputation involved ligatures or elastic bands, and rubber tubing. The only original features of the present method are the cutting of a circular groove in garden hose or building up a trough around it and drastic compression by twisting strong malleable copper wire around the protrusion. Emerson,<sup>5</sup> in 1938, stated, "Generally a piece of garden hose . . . is used." Yet he is the only author to be found who specifically mentions garden hose.

Removal of rectal prolapses by constriction has been done for years, but not often, since any one surgeon's experience with this entity is usually limited to less than 10 cases. References to the early literature on removal by constriction are covered in papers by Moschcowitz,<sup>6</sup> Reid,<sup>7, 8</sup> and Eliason and Erb.<sup>9</sup> Reid stimulated renewed interest in this type of procedure, although he limited it to cases with irreducible prolapse. The ones I have treated were all reducible, as were the ones reported in the more recent literature. According to Eliason and Erb, only 1 death from this type of operation had been recorded—in 1900. They treated 3 cases in this manner with good results at four to fifteen months. Wangersteen<sup>10</sup> reported 1 case satisfactorily man-

aged in this way with a good outcome two months later. Reid's 2 patients were cured between three and four years afterward. Anderson and Borland<sup>11</sup> had 1 case treated by the Reid technic with a good immediate result. In 1938, Emerson<sup>5</sup> recorded 2 deaths following treatment by elastic ligature and severe morbidity in 5 others, with ensuing stenosis. Thus, from the literature one would conclude that amputation of rectal procidentias by constriction is not a good procedure, since in the last twenty years there have been 2 operative deaths among 14 reported cases. There has also been considerable morbidity, as well as rectal stenosis, and the period of observation has been for the most part too short to decide about the permanency of cure.

A fairly complete review of the literature of the last fourteen years leads one to the same conclusion concerning the various other methods of treatment, both abdominal and perineal. Either the morbidity or the mortality is similar, or there is a high rate of recurrence, or good results are based on insufficient length of observation. This conclusion applies in part to my own cases, which are expected to increase and which will be followed for significantly longer periods.

The largest series of cases with apparently the best results is that of Miles.<sup>12, 13</sup> He performed surgical amputation of the protruded bowel on 34 patients, with 1 operative death and 1 recurrence at five years. Lockhart-Mummery<sup>14</sup> wrote, "For very large prolapses the best operation is amputation." Yet in 1932, Rankin, Borgen and Buie<sup>15</sup> stated, "Procedures directed toward the cure of the prolapse by resection have little to recommend them."

The objective of all methods of treatment is the formation of scar tissue between the rectum and the surrounding structures. This seems to have been well accomplished by surgical amputation and logically should be achieved just as well by compression amputation. The minimal loss of blood and the short time required are in favor of the latter technic, and succinylsulfathiazole has removed its greatest danger—namely, sepsis. The mortality and morbidity with the constriction method appear to have come from technical errors. For example, the hose has been inserted too far above the point of constriction, thus allowing the accumulation of feces between it and the rectum. Peristalsis may have forced some of this material through a weakened area in the tissues. There should not be more than a few centimeters of hose above the point of compression. Furthermore, it is probable that in some cases strangulation has not been complete, thus permitting much greater septic and toxic absorption. A slight increase in the diameter of the hose might have reduced or eliminated an undesirable amount of stenosis. From my experiences with uterine procidentias and vaginal relaxations, I am convinced that some patients have tissues so constituted as to be incapable of permanent anatomic

reposition, and that just as 15 per cent of gynecologic patients have more or less recurrence, so will there continue to be an unavoidable percentage of recurrent rectal prolapse.

### SUMMARY

Some modifications of an old method of removing rectal prolapses by compression amputation have been presented. In 5 cases of reducible rectal prolapse in women the procedure has been safe, and the results in 4 cases have thus far been good for periods varying from one year and nine months to four years and eleven months. In the fifth case, prolapse has twice recurred after twelve and eighteen months, respectively, of temporary cure.

A brief evaluation of the literature is included, with evidence that surgical amputation has yielded the best results. It is suggested that compression amputation should be just as effective, and it has the advantage of being a much simpler procedure.

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### DISCUSSION

DR. JAMES B. WOODMAN, Franklin, N. H.: Some years ago on looking up the Whitehead operation, which was in vogue at that time, I found that there was no apparatus described to put in the rectum as a form around which to do this operation, so I secured a champagne cork and fitted a heavy loop of wire in one end for a handle, introduced it and tied on heavy braided silk,—thus doing away with the necessity of putting tape there,—with excellent results. I have used this method three or four times since then.

DR. ALLEN G. RICE, Springfield, Mass.: I cannot lay claim to the invention of any ingenious gadget, but five years ago next December an engineer presented himself in the office and demonstrated with the greatest ease what his trouble was. With hardly any exertion he could extrude about 20 cm. of his rectum. He told me that he had previously had three operations, one from below and two from inside the abdomen, and that all had been failures. He wanted to know if there was anything I could do. I asked for a day or two to think it over, and when he came back I proposed the following procedure, which he accepted. I opened the abdomen and pulled up all the sigmoid until it was taut, and then did a Mikulicz type of colostomy. Later I cut the spur and closed the incision. The patient has been perfectly well ever since.

DR. E. PARKER HAYDEN, Boston: Reid several years ago described 3 cases in which he carried out this procedure, but Dr. George Smith is the only person with whom I have discussed it firsthand. I am going to ask him if he had examined the slough to see whether by any chance it included the uterus, but he mentioned in the latter part of his paper that one could palpate and explore the cul de sac, if one desired.

I have had 1 case in which the uterus was palpable in the anterior wall of the prolapse—the entire uterus. When I inspected the abdomen I was unable to see the uterus in the pelvis until I reached down with my hand and pulled it up from the depths of the cul-de-sac herniation.

I looked these cases up at the Massachusetts General Hospital several years ago and found that we had had about 1 case a year. In a period of twenty-one years there were 20 cases, operated on by many surgeons and by a variety of methods, consisting principally of the Moschowitz obliteration of the cul de sac. The mucous membrane, in some cases, had to be excised afterward because it persisted in prolapsing, and in several cases a plastic was done on the atonic sphincter. For example, one patient had had a complete prolapse for twenty years, and one year after doing both a Moschowitz and a Lockhart-Mummery procedure, because of relaxed sphincter. I trimmed the mucosa away and did a plastic on the sphincter. Compression ligature is a simple method, and I do not see why it is not a successful way of handling this condition.

Dr. Reginald H. Smithwick has done several Delorme operations with considerable success. The mucous membrane is excised in a cuff around the prolapse, after which sutures are taken in the submucosa vertically, thereby reducing the length of the prolapse until the mucous membrane edges come together, these edges are then sutured.

One can apparently treat this condition successfully by a number of different procedures, of which the method described by Dr. Smith is undoubtedly the simplest technically.

plaster was wound, leaving a trough 1.5 cm. wide and 0.5 cm. deep.

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#### DISCUSSION

Older methods of achieving constriction amputation involved ligatures or elastic bands, and rubber tubing. The only original features of the present method are the cutting of a circular groove in garden hose or building up a trough around it and drastic compression by twisting strong malleable copper wire around the protrusion. Emerson,<sup>5</sup> in 1938, stated, "Generally a piece of garden hose . . . is used." Yet he is the only author to be found who specifically mentions garden hose.

Removal of rectal prolapses by constriction has been done for years, but not often, since any one surgeon's experience with this entity is usually limited to less than 10 cases. References to the early literature on removal by constriction are covered in papers by Moschcowitz,<sup>6</sup> Reid,<sup>7, 8</sup> and Eliason and Erb.<sup>9</sup> Reid stimulated renewed interest in this type of procedure, although he limited it to cases with irreducible prolapse. The ones I have treated were all reducible, as were the ones reported in the more recent literature. According to Eliason and Erb, only 1 death from this type of operation had been recorded—in 1900. They treated 3 cases in this manner with good results at four to fifteen months. Wangenstein<sup>10</sup> reported 1 case satisfactorily man-

aged in this way with a good outcome two months later. Reid's 2 patients were cured between three and four years afterward. Anderson and Borland<sup>11</sup> had 1 case treated by the Reid technic with a good immediate result. In 1938, Emerson<sup>5</sup> recorded 2 deaths following treatment by elastic ligature and severe morbidity in 5 others, with ensuing stenosis. Thus, from the literature one would conclude that amputation of rectal procidentias by constriction is not a good procedure, since in the last twenty years there have been 2 operative deaths among 14 reported cases. There has also been considerable morbidity, as well as rectal stenosis, and the period of observation has been for the most part too short to decide about the permanency of cure.

A fairly complete review of the literature of the last fourteen years leads one to the same conclusion concerning the various other methods of treatment, both abdominal and perineal. Either the morbidity or the mortality is similar, or there is a high rate of recurrence, or good results are based on insufficient length of observation. This conclusion applies in part to my own cases, which are expected to increase and which will be followed for significantly longer periods.

The largest series of cases with apparently the best results is that of Miles.<sup>12, 13</sup> He performed surgical amputation of the protruded bowel on 34 patients, with 1 operative death and 1 recurrence at five years. Lockhart-Mummery<sup>14</sup> wrote, "For very large prolapses the best operation is amputation." Yet in 1932, Rankin, Bagen and Buie<sup>15</sup> stated, "Procedures directed toward the cure of the prolapse by resection have little to recommend them."

The objective of all methods of treatment is the formation of scar tissue between the rectum and the surrounding structures. This seems to have been well accomplished by surgical amputation and logically should be achieved just as well by compression amputation. The minimal loss of blood and the short time required are in favor of the latter technic, and succinylsulfathiazole has removed its greatest danger—namely, sepsis. The mortality and morbidity with the constriction method appear to have come from technical errors. For example, the hose has been inserted too far above the point of constriction, thus allowing the accumulation of feces between it and the rectum. Peristalsis may have forced some of this material through a weakened area in the tissues. There should not be more than a few centimeters of hose above the point of compression. Furthermore, it is probable that in some cases strangulation has not been complete, thus permitting much greater septic and toxic absorption. A slight increase in the diameter of the hose might have reduced or eliminated an undesirable amount of stenosis. From my experiences with uterine procidentias and vaginal relaxations, I am convinced that some patients have tissues so constituted as to be incapable of permanent anatomic

made to remove all the bony fragments and pieces of periosteum that lay between the forearm bones and to suture the torn soft tissues. Complete repair, however, was impossible because of the severe trauma.

The second incision, small in size, was made over the site of the ulnar fracture. It was found that the ulnar fragments

growth between the radius and ulna. It was impossible to separate the muscles without carrying away some of the periosteum. The bridge of bone between the radius and ulna was next removed, thereby restoring the rotary motion of the forearm. The muscles on each side of the interosseous space were sutured in such a manner as to cover the raw

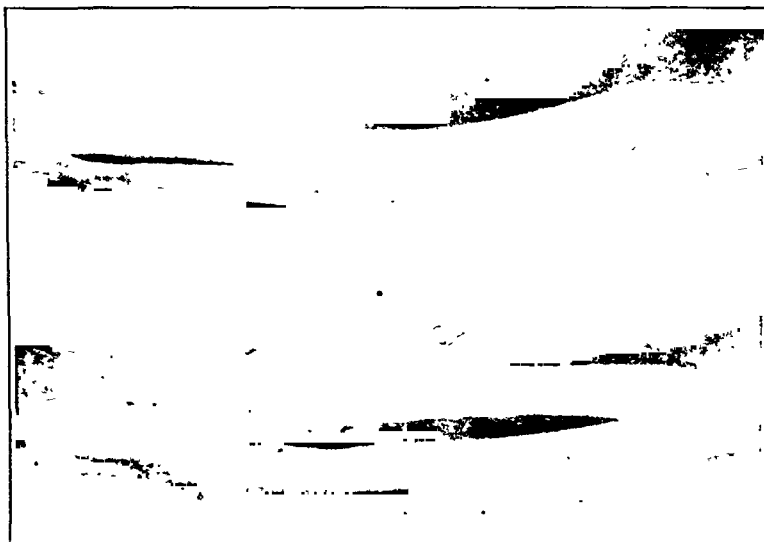


FIGURE 2. Roentgenograms Taken Over Three Years after Resection of the Synostosis and Showing No Evidence of Renewed Proliferation.

had fallen into position on the reduction of the radial fracture, and it was necessary only to secure them with chromic catgut, which was drawn through two drill holes.

An uneventful convalescence ensued. Roentgenograms taken on January 15 showed the fragments in good alignment (Fig. 1B). The vitallium plate was removed in April.

The first definite evidence of cross-union between the radius and ulna was noted in a roentgenogram taken on March 7 (Fig. 1C). In subsequent roentgenograms the bridging between the bones became increasingly dense (Fig. 1D). Clinically, rotation of the forearm was impossible. Operative excision of the synostosis was advised.

On October 11, the surgical treatment was carried out as follows. Under general anesthesia, an incision was made along the inner side of the ulna in the line of the synostosis. The muscles were split down to the interosseous space and, with a great deal of difficulty, were separated from the bony

bony surfaces. The forearm was supinated as much as possible, and a compression dressing was applied.

The patient made a good recovery. Complete range of flexion and extension at the elbow was obtained early.

When the patient was examined on January 17, 1945, three years and three months after the removal of the bony bridge, he had recovered 75 per cent of the normal rotary motion at the elbow. There was slight limitation in the motion at the wrist, owing to the presence of arthritic changes. The hand had a complete grip. A roentgenogram taken on that date showed good integrity of the interosseous space (Fig. 2).

#### SUMMARY

A case of radioulnar synostosis, with complete recovery following operative excision, is reported.

412 Beacon Street



# RADIOULNAR SYNOSTEOSIS OF TRAUMATIC ORIGIN\*

## Report of a Case

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**A**N EXTENSIVE review of the medical literature reveals that there are few recorded cases of synostosis of the forearm bones, although this is always mentioned as a possible complication in discussions of radial and ulnar fractures. The purpose of this report is to present a case of radioulnar

at the time of the accident revealed comminuted fractures of the radius and ulna, semioblique in type and situated 12 cm. above the wrist (Fig. 1A). The fractures were at slightly different levels, and the fragments were completely displaced.

In view of the severity of the trauma, it was realized at the outset of treatment that the soft tissues had undoubtedly been extensively damaged; hence, the possibility of the



FIGURE 1. Roentgenograms of Forearm.

A — This film shows the original semioblique fractures of the radius and ulna at different levels; B — this film, taken four days after open reduction, indicates that the fragments were in good alignment; C — this film, taken approximately two months after reduction, shows evidence of cross-union between the radius and ulna; and D — this film, taken about four and a half months after reduction, shows definite synostosis.

cross-union that occurred as a sequela to comminuted fractures of the forearm bones, which were accompanied by a great deal of damage to the soft tissues.

### CASE REPORT

A large, muscular 44-year-old man, while at work in a factory on January 7, 1941, caught his forearm in a moving belt, sustaining an extremely severe injury. The radius and ulna were fractured, and the distal fragments with the hand were carried beyond a right angle by the force of the belt. Only by exerting great force was the patient able to prevent the forearm's being drawn into the pulley. Roentgenograms taken

development of synostosis was considered. The danger of circulatory disturbance was also considered, because of the sclerosis of the vessels that was revealed in the roentgenograms. To permit observation and ensure circulatory stabilization, the forearm was maintained in suspension in a molded-plaster cast for 4 days.

Reduction by a closed method was not considered feasible because of the obliquity of the fragments. On January 11, I carried out an operative reduction, taking great care to prevent further traumatization. Two incisions were used for exposure. First, a longitudinal incision was made over the site of the radial fracture. The fragments were easily placed in normal anatomic alignment and made secure by applying a three-screw plate of vitallium. The membrane and periosteum were found to be badly lacerated, and small chips of bone were displaced into the interosseous space. An attempt was

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than would have been expected from the usual scarlet-fever attack rate. By the time the directions on the package were modified the reputation of the Dick toxin in pediatric practice was bad, and its use has been continued only in the hands of a few practitioners.

The immunization of pupil nurses has been so satisfactory from the standpoint of economy that the procedure is carried out in most hospital training schools. Where this procedure has been carried out with the care and scrutiny due an erythrogenic toxin derived from streptococci, the discomfort has been at a minimum. With permission of the patent holders a formalized toxin was made by the Massachusetts Department of Public Health. This did away with the discomforts, but the immunity gained was not so good as that achieved with the straight toxin. Permission to continue this investigation in Minnesota was refused.<sup>9,10</sup> As far back as 1925, several hospitals were giving eight or ten doses instead of three or five, and thereby reducing to the minimum the incidence of sore arms and febrile reactions. A general hostility toward the patent prompted some institutions to make their own toxin for this purpose. Needless to say, their methods were not published, and an unknown amount of investigative work was stifled because of the difficulty of getting permission to perform it.

Toomey<sup>11</sup> has given an excellent review of scarlet-fever immunization. The attack rate of pupil nurses varied in different years in different hospitals from 8.6 to 17.7 per cent. Among the immunized nurses the attack rate in these hospitals was 0.6 per cent. Reactions were noted in 10.2 per cent. Pupil nurses are continuously and heavily exposed on the scarlet-fever wards. Prior to immunization it was usual to have several nurses constantly sick with scarlet fever throughout the winter months. It is now rare to have one nurse lost from duty from this cause. This economic gain to the hospitals for contagious diseases over the past twenty years has been enormous.

The question is raised whether this immunity is more apparent than real. In other words, it is argued that only an immunity against the toxin is achieved, and that these immunized nurses probably act as dangerous streptococcal carriers. On the other hand, it has been asserted that there is apparently somewhat less streptococcal disease among the immunized nurses as a result of this immunization. There is no substantial evidence to support either contention. In short, immunization against scarlet fever gives rise to a specific immunity against the toxin similar to that achieved by an attack of scarlet fever, probably no more and no less. It is distinctly worth while for pupil nurses whose training includes duty on scarlet-fever wards. Beyond this, there is room for debate owing to the low morbidity and low mortality of scarlet fever.

Recently scarlet-fever immunization has been instituted in the 25 per cent of men of the Royal Canadian Air Force<sup>12</sup> found to be Dick positive. The advantages and disadvantages of this procedure remain to be seen.

One disadvantage of immunization is that in those who harbor chronic streptococcal infections or who have had rheumatic infections in the past there is a sensitiveness to the hemolytic streptococcus toxin as manifested by polyarthritides, erythema nodosum and even heart disease.<sup>13</sup> Such persons, however, would show much the same symptoms if they came down with scarlet fever. Consequently, it is better for them not to be immunized and to avoid exposure to streptococcal diseases — if such a thing is possible. Therefore, in selecting those who are to be immunized, one should eliminate not only those who are Dick negative but those whose past histories offer contraindications.

Passive immunization has been used successfully in the last twenty-five years. Immediately after exposure a dose of pooled convalescent serum or Dick antitoxin is administered intramuscularly. The protection lasts only about fourteen days.

#### FORMS OF SCARLET FEVER

It is necessary to keep in mind that the usual form of scarlet fever is the result of streptococcal infection of the upper respiratory tract. As such it is spread by direct and indirect contact, and it may also be air-borne. The dust in scarlet-fever wards is apt to be heavily laden with hemolytic streptococci, and the air is especially full of these bacteria after bedmaking and sweeping.<sup>14</sup> On the other hand, so-called "puerperal scarlet fever" results from a pelvic infection, and "surgical scarlet fever" from wound infection. Of course, the streptococci in these infections must be capable of producing erythrogenic toxin. "Burn scarlet fever" may come on at any time during the healing of an extensive burn when these hemolytic streptococci get onto the wound and elaborate their scarlet-fever-producing toxin. To these well-known forms of scarlet fever must now be added so-called "intestinal scarlet fever," which is due to the absorption of the toxin from the intestine in cases showing much gastrointestinal disturbance. The Dicks<sup>15</sup> showed that enteric-coated tablets of the toxin could give rise to vomiting and diarrhea, along with the rash. In this activity of the streptococcus in the gastrointestinal tract it may also give off an enterotoxin<sup>16</sup> that is quite apart from the toxin that produces the rash. The term "septic scarlet fever" is used when the pyogenic properties of the streptococcus are in evidence.

The Dicks<sup>17</sup> resurrected the term "*scarlatinae sine eruptione*" because in their inoculation experiments certain subjects became sick without the rash. The modern concept no longer grants any

## MEDICAL PROGRESS

### SCARLET FEVER\*

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WHEN Sydenham<sup>1</sup> coined the term "scarlet fever" in 1676, he remarked that this was a disease in name only. The truth of this statement becomes more and more apparent with the progress of knowledge of streptococcal infections. When the Dicks isolated their so-called "*Streptococcus scarlatinae*" and patented the toxin and antitoxin derived from it, the idea of a disease entity seemed to become more fixed. This patent has now expired. With the advance in the knowledge of streptococcal diseases many ideas regarding this eruptive fever have changed. Scarlet fever is not so much a disease entity as it is a manifestation in susceptible persons of a toxic substance elaborated by some strains of beta-hemolytic streptococci. Nor are the toxins elaborated from these types identical.<sup>2</sup> Not only can many different types of streptococcus produce a scarlet-fever toxin, but from the work of Aranow and Wood<sup>3</sup> it appears that certain strains of hemolytic *Staphylococcus aureus* can produce a typical scarlatiniform rash, and that they elaborate an erythrogenic toxin that is antigenically related to that produced by the streptococcus.

The sore throat of scarlet fever cannot be differentiated from any other streptococcal sore throat except that there is apt to be a bright-red enanthem on the soft palate. The eruption is much less likely to be on the face than is the case in measles and German measles. It is essentially an erythema due to engorgement of the superficial capillaries of the skin. Engorgement of the capillary tufts in the papillae gives rise to the punctate character of the rash. In a severe rash the capillaries tend to rupture, especially in the folds of the skin — the so-called "bleeding lines." The engorgement of the capillaries in the papillae of the tongue gives its strawberry or raspberry appearance. Except for the inflammation of the fauces, all these manifestations of scarlet fever are due to the action of the erythrogenic toxin on the superficial capillaries. This toxin is also responsible for the fever and the not infrequent nausea and vomiting and occasional diarrhea.

#### IMMUNITY

The Dick test is the measure of susceptibility to scarlet fever. It consists of an intradermal injection of 0.1 cc. of a standardized dilution of the toxin, with recording of the result twenty-four hours later.

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Those who are susceptible show a localized erythema and are recorded as Dick positive, whereas those who show no reaction are recorded as Dick negative. The Dick reaction is almost always negative at birth. Thus, an infant is born with immunity to scarlet fever but loses it rapidly as it approaches the second year of life.<sup>4</sup> From this age the percentage of Dick positives drops from nearly 80 per cent through the grammar-school period to somewhere between 40 and 20 per cent at the military age, according to the opportunity for exposure. This age curve of immunity as measured by the Dick test<sup>4</sup> is similar to the incidence curve of scarlet fever according to age.<sup>5</sup> Powers and Boisvert<sup>6</sup> have studied the factor of age in relation to the type of infection in streptococcosis. The incidence of other manifestations of streptococcal infections follows different patterns as regards age.

Generally speaking, the erythrogenic toxin of the many strains of streptococcus is antigenically much the same, and in the long run confers a lasting immunity. The immunologic response may be monovalent during convalescence and become polyvalent only well after recovery. In other words, the scarlet-fever patient sometimes reacts specifically to the type of organism with which he is infected. In this case, if he is exposed to another type during convalescence, he may have a relapse with a return of the sore throat, fever and rash.<sup>7</sup> On the other hand, given sufficient time, the immunity conferred by one attack usually affords protection against the toxin of a variety of strains — hence the relatively permanent immunity conferred by one attack of scarlet fever. Although the immunity conferred by a single attack of scarlet fever is primarily against the toxin, this does not of necessity include protection from subsequent bacterial invasion by the original type or any other type of streptococcus. Kuttner and Lenert<sup>8</sup> have shown that bacteriostatic properties develop in the blood of patients recovering from pharyngitis due to a single type of Group A streptococcus, and that these properties may persist for many months.

By injecting the erythrogenic toxin in repeated doses a relative immunity to scarlet fever can be achieved. This method of immunizing was begun in 1925. Unfortunately, the early dosage as printed on the preparations licensed through the Dick patent was too large and resulted in the very thing that the patent aimed to avoid, namely, bad effects from the toxin. Most pediatricians promptly discarded this procedure because it caused more illness

especially in the cervical region. The lymph nodes in the neck become swollen and tender, but if they are soft and not particularly painful no chemotherapy is indicated even though fever is present; nor are any local applications necessary. This situation represents a late reaction to the streptococcal infection, is manifested also in the axillas and groins, and subsides of itself. A hard, firm, extremely tender cervical node is quite another matter and may represent a pyogenic invasion. Here the question of chemotherapy is debatable. Chemotherapy undoubtedly controls the pus formation, but the induration remains for a long time. Sometimes it remains longer than if the sulfonamides had not been used and the node had been allowed to suppurate and point to the surface and had then been incised. The application of heat or cold has no apparent influence on the course of such suppuration, since pointing takes place under an ice bag as it does under a hot poultice. Either heat or cold may afford a definite degree of comfort.

In addition to the suppurative complications following scarlet fever, there are several others that are the result of some altered response to the causative streptococci or their products, namely, acute diffuse glomerulonephritis, erythema multiforme and rheumatic fever, the tissue changes of which are discussed by Mallory and Keefer.<sup>27</sup>

Nephritis in scarlet fever is of varying degrees of seriousness. During and following the eruptive phase an increased Addis count<sup>28</sup> is found even in the mildest cases. A mild transient albuminuria may also take place. These are both due to the irritant action of the toxin. When red cells or casts begin to show in an ordinary centrifuged specimen of urine, one must be on guard. The explosive nature of acute hemorrhagic glomerulonephritis suggests a violent antigen-antibody reaction in the glomeruli. This is apt to occur some time between the ninth and twenty-first days of convalescence. The urine on the previous day may have been quite normal. The situation is the same as that in glomerulonephritis in diseases other than scarlet fever and calls for the same treatment.<sup>29, 30</sup> Glomerulonephritis cannot be prevented by dietary regulations.

Erythema nodosum, erythema marginata and urticaria of nonserum origin are not infrequent on any large scarlet-fever service. These also are looked on as antigen-antibody reactions.

Scarlet fever has long been considered to be the origin of endocarditis. The toxin of scarlet fever does not in itself do any permanent damage to the endocardium, and only in the severest toxic cases is the myocardium injured in the eruptive phase. Scarlet fever, however, as a streptococcal disease may initiate rheumatic fever, and that is where the greatest danger of scarlet fever lies today. The exact relation of streptococcosis to rheumatic fever is not yet known, but that streptococcal infections do usher in rheumatic fever is beyond all doubt.

It was formerly thought that transient murmurs in the course of scarlet fever were of no significance.<sup>31</sup> Subsequent experience has shown that the "will-of-the-wisp" murmurs that appear in the second and third weeks are sometimes followed within four weeks by electrocardiographic indications of myocardial damage, marked murmurs and even sudden cardiac failure. These are clearly of rheumatic-fever origin. It is of great interest that rheumatic fever is apparently likelier to occur after the more superficial infections than after the deeper invasions of the streptococcus, such as erysipelas and abscess formation. Ordinary scarlet fever itself is one of the most superficial of streptococcal infections, and as such it is a dangerous instigator of that far more serious condition, rheumatic fever. It is in this capacity that scarlet fever may lead to subsequent damage of the heart valves. Furthermore, streptococcal tonsillitis is just as dangerous. Thus, the superficial infective process rather than the rash appears to be the factor involved in the instigation of rheumatic fever.

#### ETIOLOGY

The concept of the etiology of scarlet fever has undergone remarkable changes in the last twenty years. In 1924, the Dicks<sup>32</sup> incriminated a hemolytic streptococcus as the causative agent in this disease. Their work helped greatly to clear the confusion concerning the specific agent, but their term "*Streptococcus scarlatinae*," tended to oversimplify the situation. With the development of methods for the identification of streptococci according to their antigenic make-up and for the classification of these organisms according to the group-specific carbohydrate material<sup>33</sup> and type-specific nucleoproteins,<sup>34</sup> a more exact basis was furnished for the study of the organisms that produce scarlet fever. It is now known that strains that produce scarlet fever in some patients may produce only localized diseases without a rash in others, and that in various communities of a single country and in the various countries of the world the streptococci that are responsible for the production of scarlet fever may be widely different antigenically, varying to a slight degree in the type of group-specific carbohydrate that they contain, and in a much greater degree in the nature of the type-specific nucleoprotein.

All the strains of streptococcus isolated from the pharynges or other local sites of infection in cases of scarlet fever belong to the group that produce beta hemolysis, as seen by a fairly wide, well-defined, clear ring of hemolysis about the colony in blood agar media. Analyses according to the method of Lancefield<sup>35</sup> of many strains for the type of carbohydrate that they contain have shown that more than 95 per cent of them belong to her Group A, the group that is known to be by far the most prevalent in all infections in man due

such term. Without the rash there is no scarlet fever, even though the patient is infected with a streptococcus that is causing a rash in others. Furthermore, such a patient who does not have scarlet fever is capable of giving it to those who are susceptible. To include all infections of the toxin-producing streptococci as scarlet fever is a misuse of the term, since the resistance of the host is an equally important factor. Thus, as pointed out by Gordon,<sup>18</sup> scarlet fever is not just a problem of identifying a rash. From the clinical and epidemiologic standpoint, much depends on where the infection is situated, on the type of streptococcus and on the resistance of the host.

It is obvious that dissemination of these streptococci is greatest in those cases in which the infection is in the upper respiratory tract. In the puerperal form the infected discharge is fairly well confined by the pads over the vagina, especially when these are disposed of by the proper technic and bedpans are sterilized. The dressings of wounds and burns permit the least possible dissemination of infected material. Thus, with good modern surgical technic, a case of scarlet fever originating on a maternity or surgical ward rarely gives rise to a second case. Prompt isolation of the patient makes it unnecessary to quarantine the ward. On the other hand, when upper respiratory scarlet fever breaks out on a maternity or surgical ward, there is much more opportunity for the dissemination of the streptococci.

#### TREATMENT

Scarlet-fever antitoxin is the specific measure to combat the eruptive manifestation of this disease in that it neutralizes the erythrogenic toxin. Thus, the degree of toxicity manifested in the patient is the indication for this antitoxin, which may be administered intramuscularly or, in a severe case, intravenously, in the form of a polyvalent horse serum (Dick). In moderate cases, a patient under 50 pounds in weight should receive 8000 units, and in severe cases 16,000 units. In those over 50 pounds one should give 16,000 units in moderate cases and 32,000 units in severe ones. Pooled convalescent serum given intramuscularly or intravenously is also efficacious. Here a patient under 50 pounds gets 20 cc. in mild cases and 40 to 60 cc. in severe cases, whereas for those over 50 pounds the dose is 40 cc. in moderate cases and 60 to 100 cc. in severe ones. If given in the first forty-eight hours both these serums show a prompt and beneficial action. The temperature usually drops abruptly, the rash fades, and the sore throat subsides. Occasionally one sees no appreciable effect even with early treatment; in other cases dramatic response may be achieved as late as the fourth day. Serum therapy is unnecessary in mild cases, and is of no value in late septic complications.<sup>19,20</sup> The concentrated gamma globulin fraction from pooled normal plasma has been used in the eruptive phase, but judging from our observations the results in its present form are inconstant.

Sulfonamide therapy does not neutralize the toxin and therefore has no effect on the eruptive phase.<sup>19-21</sup> The temperature is not materially lowered, and the duration of the rash is not shortened. The sulfonamides do tend to control the further invasion of the streptococcus, and they definitely control the pyogenic activity of the streptococci if and when such activity is in evidence. In mild and moderate uncomplicated cases, when sulfonamides are given for the duration of the fever only, no appreciable benefit has been noted by most observers when adequate controls have been instituted.<sup>22</sup> In severe cases with evidence of deep invasion of the throat, serum therapy should be given along with sulfonamides.

If sulfonamide therapy is instituted at the start in adequate dosage to give a level of approximately 6 mg. for the first four days, and a maintenance dose of half that daily dose is continued for another four days and halved again for the next eleven days, the pyogenic complications are reduced. Nevertheless, one must not be surprised if suppurative otitis media and suppurative cervical adenitis develop in spite of this treatment.\* Furthermore, drug rashes and drug fevers occur in certain patients to baffle the clinician, and in rare cases severe anemia develops rather suddenly and requires blood transfusions. In any event, the nonpyogenic complications are not avoided.

#### COMPLICATIONS

The complications of scarlet fever constitute the manifold expressions of streptococcosis. From the upper respiratory tract may develop sinusitis, especially ethmoiditis, which may be particularly prominent in certain epidemics. This, like suppurative otitis media, represents bacterial invasion with pus formation. The accepted therapy of all pyogenic manifestations is full dosage of sulfadiazine or sulfamerazine. If, after withdrawal of the drug, a discharge from the ear returns, it is well to consider the possibility of a mastoiditis. Here one must keep in mind that sulfonamide therapy may hold back a leukocytosis and mask the x-ray findings.<sup>23</sup> The postponement of surgery may delay recovery. Surgical mastoiditis has been greatly simplified by the local use of sulfonamide drugs, and more recently by the use of penicillin.<sup>24</sup> Severe tonsillitis, pharyngitis, laryngitis, pneumonia, empyema, meningitis and bacteremia call for intensive sulfonamide or penicillin therapy. In the presence of rheumatic fever, penicillin is to be preferred for the treatment of the suppurative complications.<sup>25,26</sup>

A generalized lymphadenitis is a frequent accompaniment of scarlet fever. This occurs early in the disease as a result of the circulating toxin. Later on, between the tenth and the twenty-first day, there may be a recrudescence of lymphadenopathy,

\*The widespread use of sulfonamide therapy and prophylaxis may be responsible for the development of sulfonamide-resistant strains of streptococci during an epidemic of scarlet fever.

type of toxin have been described. Some of them have been isolated from other cases of osteomyelitis, and one from the pharynx of a patient who had a typical case of scarlet fever. Thus the present concept of the etiology of scarlet fever extends even beyond the Group A streptococci.

A rational concept of the etiology of scarlet fever appears to be one in which it is recognized that with certain rare exceptions the beta-hemolytic streptococcus is the agent that is responsible for the disease. It is usually Group A organisms that are responsible, however, and practically any of the forty-six serologic types of the Group A streptococci that have been identified may produce the disease, the predominant type varying with the year, the community and the country.

All the serologic types of the Group A streptococcus that produce scarlet fever have one property in common, namely, the ability to produce erythrogenic toxin. Lack of this toxin renders a strain incapable of producing the rash that characterizes scarlet fever. The mere ability of a strain to produce this toxin, however, does not necessarily imply that it will produce scarlet fever in every person in whom it gains a foothold. The immune state of the infected subject against erythrogenic toxin is the other determining factor. Thus, people who have an antitoxic immunity (Dick negative) develop only localized streptococcal infections without a rash, whereas those who have no antitoxic immunity (Dick positive) develop a scarlatinal rash. It is a well-established fact that many of the strains that produce only localized infections without a rash in certain people are capable in the test tube of producing erythrogenic toxin, which when injected into a susceptible (Dick-positive) person produces the typical reaction. Thus, a Dick-negative person with a localized infection — without a rash — can infect a Dick-positive one, who breaks out with scarlet fever.

Although the production of erythrogenic toxin appears on the surface to be the one property that all the streptococci that produce scarlet fever have in common, this point requires qualification, since it has been shown by Hooker and Follensby<sup>2</sup> that strains of streptococcus isolated from scarlet fever may produce two different types of erythrogenic toxin, A and B, which are distinguishable on the basis of both chemical and immunologic criteria. They have shown that a single toxigenic strain may produce A or B, both or neither. This difference in the quality of erythrogenic toxin produced by different strains of the hemolytic streptococcus is thought by these authors to be a possible explanation of the fact that some persons do not become Dick negative after having had scarlet fever, and that occasionally even the early administration of potent

antitoxin does not appear to alter the toxic manifestations of scarlet fever in certain patients.

(To be concluded)

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to the streptococcus. Although this evidence points to a marked degree of similarity between all the strains of streptococci that are isolated from cases of scarlet fever, such a generalization cannot be made because other groups — namely, Group C<sup>35</sup> and Group G<sup>36</sup> — have been shown to be capable of producing the same disease, although much less frequently than Group A. In any event, as pointed out by Brown and Schaub,<sup>37</sup> *Str. scarlatinae* is not the streptococcus of scarlet fever but is a streptococcus of scarlet fever.

That no single strain of streptococcus is involved in the production of scarlet fever becomes evident from the studies on the type-specific nucleoprotein present in strains of streptococci isolated from different cases of scarlet fever. Keefer and his co-workers<sup>38</sup> analyzed the literature on the distribution of the various types of streptococci demonstrable in scarlet fever and studied a large group of cases that came under their own observation. Their conclusions were that scarlet fever may be due to a wide variety of streptococci and that the predominant types may vary from one country to another, from one community to another and from year to year in the same community or country. They found that during an epidemic in a community one type predominated or two types thrived simultaneously. They also found that as an epidemic of scarlet fever progressed in the same community, one type might be replaced later by another. This same fact was noted last year at the Haynes Memorial Hospital, where early in the winter the predominant type isolated from cases of scarlet fever was Type 1, although there were six or seven other types present. In the spring and late winter, Type 2 became the organism most frequently isolated, although some cases were still due to Type 1. Keefer and his co-workers also point out that in sporadic cases of scarlet fever the infections are oftener due to types that are not concerned with the types causing the epidemic and that there is often wide scattering. They also state that the same type of streptococcus may be responsible for different clinical diseases — that is, scarlet fever in one person, tonsillitis in another, erysipelas in a third and rhinitis in a fourth — and that when one or more types are predominant in any community, the same types are usually isolated from persons with various diseases, such as scarlet fever, tonsillitis and otitis media. All the studies made during the last two or three years in various Army and Navy establishments have borne out the same fact; in other words, in any large group of men scarlet fever may be due to a number of different types of streptococci, although one or two types are usually found to predominate.<sup>39</sup>

In view of the ample evidence that the causative streptococcus in scarlet fever may differ not only in the type of group-specific carbohydrate content but much more frequently in the qualitative character of the nucleoprotein content, it appears that

the concept of a single species of organism is hardly tenable. Furthermore, the facts that the organisms isolated from cases of scarlet fever are beta hemolytic streptococci and that they all produce erythrogenic toxin and may show similar fermentative ability do not constitute enough evidence to class them as a single species, particularly since it has been well demonstrated that they differ antigenically. The situation is somewhat analogous to that which prevails in the *Salmonella* groups. Although several strains of this group may cause acute enteritis, may be isolated from the feces of various persons and may show closely similar activity against carbohydrates, they are not classified as a single species. Indeed, they are separated into different species on the basis of an analysis of their antigenic constituents. Whereas in the case of the *Salmonella* group a specific name is usually attached to organisms that resemble each other closely in their invasive, cultural and biochemical activities, such a procedure is not necessary with the Group A beta-hemolytic streptococci, the type number sufficing to identify the organism.

The whole problem of the etiology of scarlet fever is further confused in view of the fact that organisms other than beta-hemolytic streptococci at times produce the same symptom picture. Many drugs, notably quinine and the sulfonamides, are capable of producing fever and a typical scarlatiniform rash in hypersensitive persons, followed by desquamation. These drug rashes, however, do not represent the invasion by an infectious agent, and therefore do not come under the concept of scarlet fever. Moreover, Aranow and Wood<sup>3</sup> point out that some strains of hemolytic *Staph. aureus* are capable of producing a symptom picture that is indistinguishable from clinical scarlet fever. They have described a case of osteomyelitis due to a strain of *Staph. aureus* in which a diagnosis of scarlet fever was made on admission to the hospital because the patient had a typical scarlatiniform rash and a raspberry tongue. No beta-hemolytic streptococci were cultured from the pharynx, but convalescent scarlet-fever antiserum was administered, and this blanched the rash. It was subsequently shown that the patient had osteomyelitis of the femur due to a strain of *Staph. aureus*, which was also cultured from the blood stream. Later the patient showed desquamation typical of the convalescent stage of scarlet fever. A study of this staphylococcus showed that it produced erythrogenic toxin that was closely related immunologically to that produced by some strains of beta-hemolytic streptococci. That this is not an isolated case of production of erythrogenic toxin by *Staph. aureus* is shown by a review of the literature on this subject by these same authors, who cite several other investigators who have demonstrated the production of a rash-producing toxin by a staphylococcus; at least forty-three strains that produce this

it should be considered negligence not to take x-ray films of the chest in a man with a story such as this, just as it is considered negligence to make a negative diagnosis of fracture following injury without x-ray examination.

In carcinoma of the bronchus by far the most frequent early signs are pain in the chest, blood spitting and cough; the cough is usually brassy and unproductive. This man did not have pain in the chest and did not have any blood spitting, and the cough was said to be loose. All these facts are against

have had an extensive suppurative process in the lungs. He had a low blood pressure on two occasions. I shall come back to that later.

The examination of the blood — the hemoglobin level, white-cell count and so forth — was within the limits of normal.

It is surprising how little the anteroposterior film (Fig. 1) shows, and one wonders why there were such definite signs on percussion over the left side of the chest. If you look at the lateral view you can see there is dullness in the posterior part of the

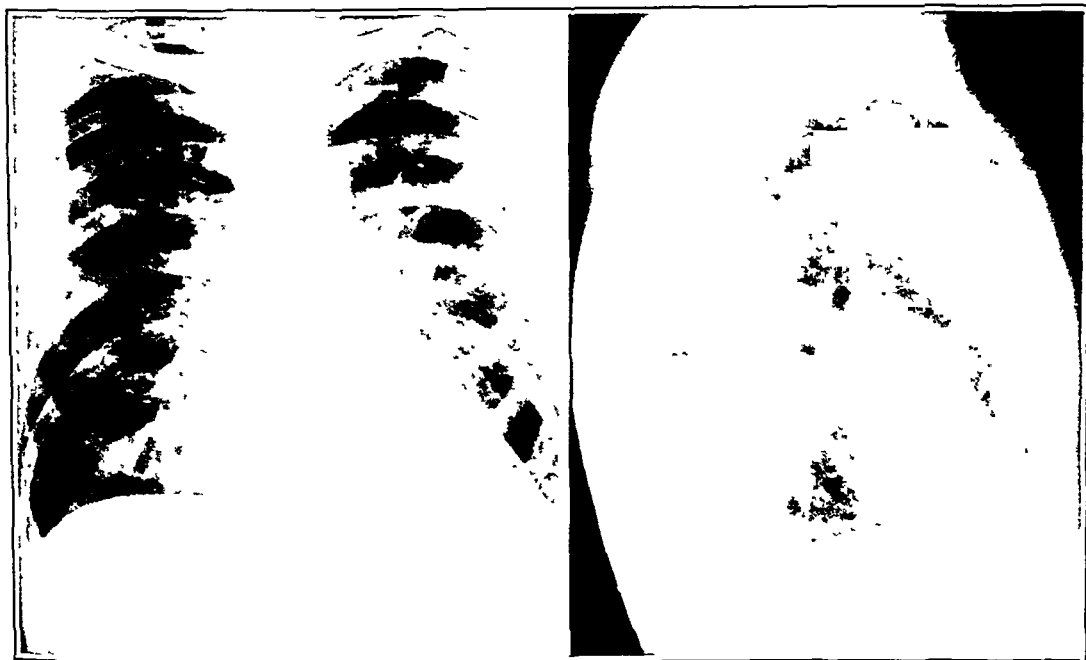


FIGURE 1. Anteroposterior (left) and Lateral (right) Roentgenograms of Chest.

carcinoma of the bronchus and in favor of some other cause, possibly tuberculosis.

The story was always one of weakness and malaise, which are not unusual complaints for carcinoma of the bronchus. In the family history they mention locomotor ataxia. He was married and had three children and later on had a negative Hinton test. I do not think we have to pay much attention to syphilis.

What do we get out of the physical examination? He was emaciated and had a cough and limited chest expansion. The statement about the percussion note is interesting. I wonder whether that interpretation would be a help or a hindrance to a clinical man. What do you think about it, Dr. Cass?

DR. JOHN W. CASS: I should say that it was simply a sign of bronchial obstruction.

DR. HOLMES: He had an expiratory wheeze. That is the most significant of all the physical findings. Expiratory wheeze means bronchial obstruction. He had no pain, and no elevation of temperature, pulse or respiration. It seems unlikely that he could

chest in the region of the lower lobe. Then, if you look carefully at the left lung in the anteroposterior film you notice that it is brighter than the other side and that the number of markings in the lung are less than those on the other side. In other words, there is evidence of collapse of the left lower lobe. The lobe is hidden behind the heart shadow. It would be helpful if films had been taken with more exposure and, perhaps, a grid film, to determine the outline of the diaphragm. If the lung is collapsed the outline of the diaphragm is obscured. It would also be helpful to know if there were any cavities in that portion of the lung. In addition, there are these massive shadows at the left lung root. They are probably due to enlarged hilar nodes and are of considerable importance in the diagnosis and also when considering the question of operability. There is no evidence of calcium deposits in any of these nodes, and no calcified masses anywhere in the lung, which is some evidence against tuberculosis.

In a patient with a long story of bronchial obstruction one always has to think of an adenoma, a benign tumor of the bronchus, but this patient's



# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31181

#### PRESENTATION OF CASE

A fifty-six-year-old railroad fireman was admitted to the hospital because of malaise, weight loss and cough.

About twenty months before admission he had lobar pneumonia, which kept him in bed for two weeks. After three months he had recovered and felt quite well, but he never regained his full strength or weight. He returned to work despite the fact that his physician told him there was something wrong with his left chest. Eleven months before admission he suddenly developed malaise, loss of energy and ambition. At that time he was found to have a systolic blood pressure of "about 80" and he was given some medicine. After three weeks he improved and returned to work. He remained active until two months before admission, when he again experienced acute malaise and weakness of a severer nature than that of nine months before. This lasted three weeks. A third attack of weakness and malaise began one month before admission, and the patient remained in bed most of the time for about two weeks. Ever since the episode of pneumonia he had had a chronic "residual" cough which, especially in the morning after arising, was productive of white and gray-brown sputum, which was not malodorous and contained no blood. The cough was worse when he lay on his left side. One week before admission he began to wheeze on exertion. During the two years before admission he had lost about 35 pounds.

In the past he had had mumps, influenza and an infrequent cold. He was a moderate smoker and drank only an occasional glass of beer. His mother had died of diabetes, and his father of "locomotor ataxia." His wife and three children were living and well.

Physical examination revealed a rather emaciated man with an occasional loose cough. The heart sounds were faint and regular. There was slightly limited chest expansion on the left. The percussion note over the left base, both anteriorly and posteriorly, was duller than that on the right. There were diminished to absent tactile fremitus, breath sounds

and voice sounds in the left chest anteriorly and posteriorly, extending from the mid-upper chest to the base. Expiratory wheezes were heard over the entire chest. The throat was normal. Abdominal and rectal examinations were negative.

The temperature, pulse and respirations were normal. The blood pressure was 100 systolic, 74 diastolic.

Examination of the blood showed a red-cell count of 5,250,000, with 15.1 gm. of hemoglobin, and a white-cell count of 12,300, with 85 per cent neutrophils. The serum protein was 6.6 gm. per 100 cc., and the nonprotein nitrogen 21 mg. A Hinton test was negative. An x-ray examination of the chest revealed the left hilus to be markedly increased in size. There was an area of increased density extending downward and posteriorly into the lower lobe. Within this area several rounded masses were seen (Fig. 1). The motion of the diaphragm was paradoxical, and the mediastinum shifted to the left on inspiration. The right lung appeared normal.

On the second hospital day a bronchoscopy was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. GEORGE W. HOLMES: This story and the x-rays are typical of bronchial obstruction. In fact I think at the start that we can assume that this condition existed, and we must try to analyze the causes of bronchial obstruction. The most frequent cause is bronchiectasis, the next is tuberculosis, and the third, some form of primary neoplasm. In addition, bronchial obstruction is sometimes due to metastatic tumor and also to a foreign body. Let us go over the history with these things in mind and see if it will help us to arrive at a diagnosis.

This man was fifty-six years old, so that he was in the cancer bracket. He worked as a fireman and presumably was exposed to coal dust and other irritants. In the history it says that he was a smoker, but it does not say what he smoked: I think it makes a difference if one smokes cigarettes or a pipe. The record states that he had pneumonia and went to bed, but we are not told any of the details; in fact, we do not know whether he really had pneumonia. A story of pneumonia often follows bronchial obstruction. It really does not help us much in determining the cause of the obstruction. Carcinoma of the bronchus is frequently preceded by a story of pneumonia, and so are various other causes of bronchial obstruction. Following this episode he never regained his former weight, and the doctor warned him that he had something wrong with his chest. One wonders why the doctor did not go farther and find out what he had in the chest. Perhaps he did try, or the patient may have refused further study. Two years had passed before he came into the hospital, and all that time it was known that he had something wrong with his chest. I think that we have reached a period in chest examinations when

\*On leave of absence.

After several months' consideration he re-entered the hospital for lobectomy.

DR. SWEET: There are one or two interesting things about this case. I do not believe that he ever had paradoxical motion of the diaphragm, because it seemed to be quite active at operation. Another point is that the x-ray picture shows the anatomic findings with great accuracy. The aerated lung on the left side was the upper lobe, which filled the left chest except for one large bleb about the size of the palm of my hand. Because of Dr. Benedict's bronchoscopic findings, and having been told that the lesion was close to the upper lobe, I was extremely careful in doing the operation to search for tumor and was prepared to do a pneumonectomy. Dr. Evarts Graham\* says that it should be done on all these patients, but in this clinic we believe that a lobectomy, if it includes the entire tumor, is sufficient. He believes that the histology indicates that such tumors are potentially malignant.

DR. BENEDICT: All bronchoscopies except the first one showed that most of the tumor was in the lower lobe.

DR. SWEET: Because of that, after removing the lobe, I looked down the bronchus, with the bronchus open, and made sure that there was no tumor.

DR. CASTLEMAN: The shrunken left lower lobe that we received showed no evidence of tumor. In other words all the tumor had been removed bronchoscopically, so far as we could tell grossly, and this was confirmed microscopically. The lobe, however, was irreparably diseased with extensive bronchiectasis. The upper half of the lobe was collapsed, and there was beginning fibrosis. In the lower portion there were cystic bronchiectatic cavities measuring up to 2.5 cm. in diameter. I think that it is a good idea to remove these diseased lobes, even though some of the patients have no symptoms. We had one young boy who had an adenoma almost completely removed. He had ten to fifteen bronchoscopies over a period of years, but the left lung remained collapsed. He went into the Army and died about seven or eight months later of amyloid disease, owing to the chronic infection that he continued to have in the obstructed lobe. It is also interesting that this boy had a metastasis in a bronchial lymph node.

I agree with Dr. Sweet that the large majority of these patients do not develop a malignant tumor, but we have had 2 cases in our series of about 40 in which the regional nodes were involved with the same benign-like adenoma as the primary tumor: in neither of these cases had it gone beyond the regional nodes. Such tumors act much like the argentaffin or carcinoid tumors in the small intestine, which occasionally have metastases to the regional nodes, producing small-bowel obstruction,

but rarely go any farther. The metastasis may remain in that location for years.

DR. HOLMES: The bronchiectasis followed the adenoma?

DR. CASTLEMAN: Yes; it was a secondary bronchiectasis.

DR. HOLMES: Is it not unusual for patients with this type of tumor to be so free from fever?

DR. SWEET: The patient did have several attacks of so-called "pneumonia."

DR. HOLMES: The X-ray Department failed me by observing paradoxical motion of the diaphragm, which he did not have.

DR. SWEET: I tried to point that out.

DR. BENEDICT: Dr. Edward Churchill always believed that this patient had carcinoma, and even after bronchoscopy and after the pathological report of adenoma came back, he was still inclined to believe that it was a carcinoma because of the x-ray findings.

DR. HOLMES: That one statement of paradoxical motion would also have prevented me from accepting the diagnosis of adenoma.

DR. CASTLEMAN: The enlarged hilar lymph nodes were undoubtedly inflammatory. There are later x-ray films that do not show them.

DR. SWEET: At operation they were not particularly significant.

DR. BENEDICT: The sharp, freely movable carina by bronchoscopy at the end of two years was against carcinoma.

DR. CASTLEMAN: The patient probably did not have as much bronchiectasis at the time the first films were taken as was found in the resected lobe; it must have increased during the six years that intervened.

## CASE 31182

### PRESENTATION OF CASE

*First admission.* A twenty-four-year-old man was admitted to the hospital complaining of massive hemoptysis.

At eight years of age the patient was acutely ill with joint pains, severe chest pain, fever and malaise. A few weeks later he developed chorea. He was maintained on strict bed rest in a hospital for ten months. He had prolonged elevation of pulse and temperature, but improved gradually with rest and routine care. He was seen in the Cardiac Clinic of the Out Patient Department at the age of twenty years. He worked every day with a prescribed half hour of rest every noon and had no complaints. A physical examination at that time revealed a fairly muscular young man, with a slightly sallow complexion. The lungs were clear. The heart was enlarged, the apex beat being 9 cm. from the midline in the left fifth interspace. A systolic thrill was readily felt to the right of the sternum in the

\*Graham, E. A. Problem of so-called adenoma of bronchus. An unpublished paper presented at a meeting of the American Association for Thoracic Surgery, Chicago, May 5, 1944.

history was only two years in duration, which is about the duration for a carcinoma of the bronchus. Adenoma of the bronchus is usually associated with a certain amount of infection, and the patients have a story of raising foul sputum. I cannot rule out an adenoma of the bronchus, but I doubt that that is what he had. I do not believe that we have to consider bronchiectasis seriously, for the same reasons.

Metastatic malignant tumors, including lymphoma, have to be considered. We have had only one case that I know of in which the mass produced compression of the bronchus. As a rule, metastatic tumors of the lung do not cause bronchial obstruction.

That brings it down to whether or not this patient had primary carcinoma of the bronchus or tuberculosis, or both. There is another point in the history that we must consider at this time, that is, the low blood pressure and the story of malaise and weakness coming on at varying intervals and finally bringing him into the hospital. This low blood pressure and a process in the lungs that could be either tuberculosis or cancer makes one think of something involving the adrenal glands. Metastases to the adrenal glands are not rare in carcinoma of the lung, and their involvement is quite frequent in tuberculosis. So again we are left in the same predicament. We do not know whether this was carcinoma or tuberculosis.

Then in the x-ray examination there is something quite significant. He is said to have had paradoxical movement of the diaphragm. That probably means paralysis of the phrenic nerve, which is a fairly frequent occurrence in carcinoma and rarely occurs in other conditions. We have one case reported in which there was paralysis of the phrenic nerve with tuberculosis. This, of course, may be that case. I should like to be absolutely certain about that statement. One would think it would be a hard thing to miss, but it is not. The whole differential diagnosis, or a large part of it, so far as I am concerned, depends on that single statement.

Was any sputum obtained?

DR. BENJAMIN CASTLEMAN: No sputum examination is recorded.

DR. HOLMES: It is an important examination, and we might be able to clinch the diagnosis between carcinoma and tuberculosis on that alone.

Leaving aside the fact that cases selected for this conference are sometimes rare, one must arrive at the conclusion that this patient had a primary carcinoma of the bronchus, with changes of some sort in the adrenal glands.

The record stops at the bronchoscopy. I should like to go a step farther and speculate what should have been done about this man. In the first place I think that he should have had x-ray films taken within a month after the first episode and that he should have had a bronchoscopic examination at

about the same time. On the data that we have here he was inoperable so far as cure is concerned, because the nodes were involved. There is evidence that he may also have had involvement of the adrenal glands. Should he have had x-ray treatment? We do it usually to relieve symptoms rather than with the hope of cure. This man had no symptoms that could be alleviated by radiation.

DR. RICHARD H. SWEET: In regard to the paradoxical motion of the diaphragm, do you think that that would be the case if there had been no evidence on the x-ray films? I assume that the diaphragm was not high on the left side. In other words, I am inclined to doubt the observation.

DR. HOLMES: The fact that the diaphragm was not high makes you doubt the observation?

DR. SWEET: Yes.

DR. EDWARD B. BENEDICT: Bronchoscopy showed the carina to be normal, sharp and not fixed. At a point in the region of the orifice of the left upper lobe there was a smooth, pearly-gray mass, apparently arising from the upper lobe orifice, which partially occluded the left main bronchus.

#### CLINICAL DIAGNOSIS

Carcinoma of lung.

#### DR. HOLMES'S DIAGNOSIS

Bronchial obstruction due to primary carcinoma of bronchus.

#### ANATOMICAL DIAGNOSIS

Bronchial adenoma.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The biopsy specimen showed that this was a benign bronchial adenoma. Dr. Benedict followed the man from then on.

DR. BENEDICT: I followed him at frequent intervals. He had eleven bronchoscopies over a five-year period, and on almost every occasion I found some tumor tissue, which I removed and sent to the laboratory, with a report of "benign adenoma" each time. In the meantime, the bronchial obstruction was relieved and he was symptomatically entirely well, except for a slight morning cough. He gained weight and returned to full-time work. We thought that behind the adenoma in the left lower lobe there were collapse and bronchiectasis. In a younger man we would have advised lobectomy, but in this patient, because of his age and the absence of symptoms, we went ahead observing him bronchoscopically. Each time there was evidence of adenoma. Because of the possibility that there was an extrabronchial adenoma and because some of the cases reported in the literature occasionally show a low-grade malignancy I finally put it up to the patient to have a lobectomy to get rid of the tumor and the irreparably damaged left lower lobe.

week the sedimentation rate was 0.7 mm. per minute and the PR interval was 0.22 second. He had frequent severe hemoptyses. His white-cell count varied from 5000 to 12,000, and the red-cell count rose from 3,600,000 to 5,300,000 on discharge. The urine was negative. The cardiothoracic ratio was 18.2:30.3. X-ray examination of the lungs was consistent with pulmonary edema or congestion. An electrocardiogram showed an inverted T<sub>2</sub> and a

The lungs presented a few fine rales, and the heart almost reached the anterior axillary line. During the first few hours after admission he coughed up 400 cc. of blood, and smaller amounts on the succeeding three days. The red-cell count fell to 3,800,000. Electrocardiographic and x-ray studies showed no heart or lung changes. The temperature, the pulse and the respirations returned to normal on the fourth hospital day, and a slow blood transfusion

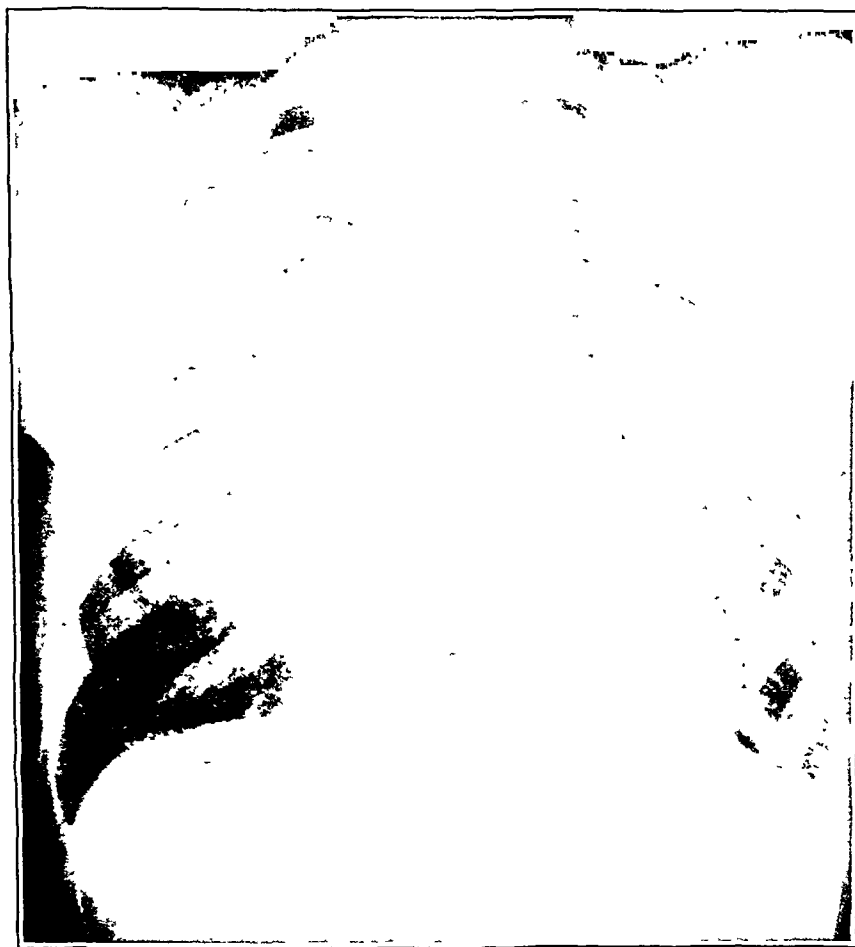


FIGURE 1. Roentgenogram of Chest.

*Note the fine nodular density throughout the lung fields, as well as diffuse increased density centrally in each field.*

tall T<sub>2</sub>, with a PR interval of 0.21 to 0.26 second. Physical examination of the heart was unchanged. The lungs cleared fairly well before discharge.

*Third admission* (ten months later). The patient developed another cold with sore throat and was readmitted to the hospital after several episodes in rapid succession of hemoptysis up to 200 cc. of bright-red blood. The ten-month interim had been almost entirely free from hemoptyses and the lungs had been clear. He had done no work, however.

The temperature was 104.2°F., the pulse 140, and the respirations 30. The blood pressure was 100 systolic, 34 diastolic.

was given. He was discharged on the twentieth day, nearly two weeks after the last hemoptysis.

*Final admission* (twelve months later). The patient worked for a few months as a painter, then went to Florida to rest. He returned by bus and, while en route to Boston, had the first hemoptysis that he had experienced in twelve months. On the day of admission he coughed up about 500 cc. of bright-red blood.

The temperature, pulse and respirations were normal. The blood pressure was 110 systolic, 50 diastolic.

An electrocardiogram showed partial auriculo-

second interspace. An apical systolic and a mitral diastolic rumble without a presystolic phase were present. A loud, rough aortic systolic murmur associated with a thrill and an aortic diastolic murmur were heard. The pulmonic second sound was prominent, and the aortic was absent. The blood Hinton and Wassermann tests were negative. The temperature and respirations were normal. The blood pressure was 100 systolic, 60 to 40 diastolic. There was a Corrigan pulse, with a regular rate of 80. During the following three years he made frequent visits to the Out Patient Department and showed little change. The heart size increased slightly, and his blood pressure was 118 systolic, 70 diastolic. He was able to climb two or three flights of stairs without dyspnea, and managed to work regularly at jobs that did not require much physical exertion. He smoked one package of cigarettes daily. He came to the Medical Clinic of the Out Patient Department at the age of twenty-three, complaining of expectoration of bright-red blood, unmixed with sputum. The first attack had occurred suddenly at 10:30 p.m., three days before admission. There were no premonitory symptoms, and he had not been exerting himself unduly at the time. The attack consisted of a choking sensation without dyspnea, followed by coughing and expectoration of about one cupful of blood. This episode lasted five minutes, then ceased abruptly, and was not associated with any discomfort. During the month preceding these episodes he had changed from automobile driving to pick-and-shovel work because he could find no other job. Physical examination at that time revealed a slight increase in the size of the heart, which extended by percussion to 11 cm. from the midsternum in the left fifth interspace. A snapping first sound at the apex, which occasionally became weak and muffled without respiratory relation, was preceded by a crescendo presystolic murmur. The systolic murmur at the apex was unchanged. No second sound was heard at the apex or over the aortic area. The diastolic murmur over the aortic area and to the left of the sternum lasted throughout diastole. A loud and extremely rough systolic murmur was present to the right of the sternum in the second, third and fourth interspaces. The rate was regular at 64, except for an occasional premature systole. The blood pressure was 108 systolic, 60 diastolic. The lungs were normal, and there was no clubbing of the fingers, and no edema. The liver could not be felt, and the neck veins were not distended. Careful examination revealed no evidence of oral or nasopharyngeal bleeding. The red-cell count was 3,800,000, and the hemoglobin 55 per cent. X-ray examination of the chest revealed enlargement of the heart in the region of the left ventricle. The aorta and lungs were normal. An electrocardiogram showed a tendency to right-axis deviation; the PR interval was 0.19 second, and  $T_3$  was inverted. Following

this examination the patient did not come to the Out Patient Department for nearly two years when, at the age of twenty-five, he returned. He had had hemoptysis almost every day for the preceding week, producing from half to one cupful of bright-red blood on each occasion. He had a "chest cold," felt weak and experienced dyspnea on exertion and slight orthopnea. He was quite pale, with a red-cell count of 3,980,000 and a hemoglobin of 8.2 gm. A few crackling rales were heard over the lungs anteriorly and posteriorly. Physical examination of the heart was as last described. The blood pressure was 95 systolic, 50 diastolic. There was no venous distention, clubbing of the fingers or enlargement of the liver. There was slight pitting edema of the lower portion of the legs. He was digitalized and given Mercupurin and ferrous sulfate. Fluids and salt were restricted. On this regime the patient improved and returned to work. Seven months later the patient was admitted to the hospital because of recurrent hemoptysis. On the preceding day he had contracted an upper respiratory infection and on the day of admission had had repeated coughing spells with hemoptysis. Shortly before admission he had a shaking chill.

On examination the patient was slightly cyanotic, dyspneic and orthopneic and had slight neck-vein distention. The heart revealed no change. There were crepitant rales over the upper lobes, and loud gurgling rales over both bases anteriorly and posteriorly. The liver could be felt at the costal margin and was slightly tender.

The temperature was 103.6°F., the pulse 84 and the respirations 36.

X-ray examination of the chest revealed a homogeneous area of increased density occupying the middle third of both lung fields from the hila to the lateral chest walls; there was no evidence of fluid (Fig. 1). An electrocardiogram revealed a PR interval of 0.20 second;  $P_1$  and  $P_2$  were prominent, and the axis was borderline. He responded well to intravenous sulfadiazine, as well as Cedilanid and an oxygen tent. The temperature was normal on the third day, and the chest cleared promptly. Several sputum and blood cultures were negative. He was discharged on the tenth hospital day.

*Second admission* (two months later). Two weeks after discharge he returned to the Out Patient Department after several episodes of hemoptysis, and because he had a "chest cold." The cough was worse when he was recumbent. There was no evidence of right heart failure. More rest, continued digitalis and diuretics were prescribed. He was subsequently readmitted to the hospital because of hemoptysis that was severer than any previous attack of bleeding. This episode again followed the onset of a "cold" and produced "almost a quart of blood."

During a two-month interval in the hospital he was afebrile after the third day. During the first

for a period of several years. Hemoptysis of this degree is not often seen in any sort of intrinsic pulmonary disease, such as tuberculosis, bronchiectasis or new growth. Hemoptysis may occur frequently in these conditions but is rarely so massive. Furthermore, since the lungs were apparently normal, we can rule out the above conditions. Certainly a neoplasm should have manifested itself after a period of four years. Pneumonia, which was suspected once in this patient, was evidently not present.

Other forms of heart disease will occasionally produce bloody sputum. Left ventricular failure due to either hypertension, aortic-valve disease or coronary disease may produce pulmonary congestion and blood-streaked or pinkish sputum but rarely, if ever, does it cause massive hemoptysis of pure blood. There are other less frequent causes of blood spitting, such as aortic aneurysm, which may rupture into a bronchus and produce a massive hemorrhage but does not cause repeated attacks over a period of four years. There is no evidence of aneurysm in the x-ray films.

One diagnosis that I believe should be seriously considered is pulmonary infarction. Pulmonary infarction frequently occurs in patients with rheumatic heart disease, owing either to pulmonary embolism or to pulmonary thrombosis. There is usually, however, only a small quantity of blood coughed up in this condition, and with repeated attacks one would expect to find good x-ray evidence of either recent infarction or scarring from old infarcts. He had none of these.

Patients with mitral stenosis occasionally cough up large amounts of pure blood. The mechanism involved is not that of heart failure, but rather that of an overstrong right ventricle, which tends to flood or overcrowd the pulmonary circulation with blood that has difficulty in getting out of the pulmonary bed because of the tight mitral stenosis. Such a mechanism may lead to pulmonary congestion, to pulmonary edema or, less frequently, to the rupture of small vessels with pulmonary hemorrhage, as observed in this case, a syndrome that has been called "pulmonary apoplexy." Patients with this syndrome do not necessarily have heart failure. This patient showed no evidence of right-sided heart failure in his early attacks of hemoptysis. In fact, the precipitating cause for his attacks is not clear. Hard work is said to precipitate pulmonary apoplexy and did precede his first attacks. Tachycardia is another cause, the rapid heart rate tending to flood the pulmonary circulation, but this was not present in this case. It is interesting to note that he continued to have normal rhythm. Most patients with this syndrome do. I believe, then, that the attacks of hemoptysis were due to the mechanism described above and not to left ventricular failure.

Finally, the question should be raised whether or not this man had active rheumatic fever. He

did have partial auriculoventricular block from time to time, and the sedimentation rate was rapid on the one reading that we have. I therefore suspect that he had active rheumatic fever during his last two or three hospital entries.

DR. CONGER WILLIAMS: I agree with Dr. Wheeler's diagnosis. This man had an interesting collection of symptoms. The most mysterious thing about the syndrome of pulmonary apoplexy is the elevation of temperature, often seen but never adequately explained. We are following such cases in the Out Patient Department. I remember another case with pulmonary edema admitted to a hospital no less than six times with a diagnosis of lobar pneumonia. No one thought it odd that the man should have pneumonia so often and recover so rapidly, that is, within three or four days of the onset. It is often difficult in this disease to restrain the attending physician from giving sulfonamides.

#### CLINICAL DIAGNOSIS

Rheumatic heart disease, with mitral and aortic stenosis and insufficiency.

#### DR. WHEELER'S DIAGNOSES

Rheumatic heart disease, with mitral and aortic stenosis and insufficiency.

Syndrome of "pulmonary apoplexy."

Active rheumatic fever and congestive failure.

#### ANATOMICAL DIAGNOSES

Rheumatic heart disease.

Acute and chronic rheumatic endocarditis of the mitral, aortic and tricuspid valves.

Stenosis of the mitral and tricuspid valves.

Cardiac hypertrophy and auricular dilatation.

Chronic passive congestion of lungs and liver.

#### PATHOLOGICAL DISCUSSION

DR. SNIFFEN: At the time of death this man was extremely cyanotic. His heart weighed 550 gm., with pronounced auricular dilatation. The mitral valve was stenotic and just admitted the tip of one finger. The aortic valve was not stenotic, but the cusps were somewhat interadherent, thickened and partially calcified. Below the aortic orifice on the posterior ventricular wall, the endocardium was rippled, like the sand on a beach, and three small accessory cusps had formed, indicating aortic regurgitation. The tricuspid valve measured 9 cm. in circumference (normal, 14 cm.), and its leaflets were somewhat thickened. On one cusp of each of these three valves there was a small area of ulceration covered by a fine layer of platelet thrombus. The

ventricular block. The heart was unchanged except for further enlargement. The point of maximum impulse lay in the anterior axillary line in the fifth and sixth interspaces. The lungs were clear. The liver could not be felt, and there was no edema. Examinations of the urine and blood were negative. The serum nonprotein nitrogen and total protein values were normal. The sedimentation rate was normal. A cephalin flocculation test was +++ in twenty-four hours.

The patient coughed up over 600 cc. of blood on all but one of the first five days after admission. After the fourth day, chest examination was difficult because of loud tracheal rales. Dyspnea and cyanosis progressed as the lung fields increased in dullness. On the sixth hospital day he expired quietly, at the age of twenty-seven years.

### DIFFERENTIAL DIAGNOSIS

DR. EDWIN O. WHEELER: Obviously this man had severe, prolonged rheumatic fever at the age of eight years. There was no further evidence of rheumatic fever for a period of twelve years.

There is not much question concerning the type of heart disease that this patient had. At the age of twenty years he presented a typical picture of rheumatic heart disease, with mitral and aortic stenosis and insufficiency and cardiac enlargement. He had no evidence of congestive failure, and he had not developed auricular fibrillation. During the next three years the mitral murmur became crescendo in character and the first sound at the apex became snapping, suggesting that the mitral stenosis had increased in severity and was of the typical adult type. The aortic insufficiency was not of marked degree. The electrocardiogram at the same time revealed an axis that was within normal limits, suggesting that the two valvular lesions, aortic and mitral, tended to balance each other so that no ventricular preponderance developed.

It is rather unusual for a patient to cough up so much blood. It was pure blood, apparently, and he had repeated attacks. There was no evidence of pulmonary congestion during the first attack. I wonder how soon after the episode of hemoptysis that observation was made. In a patient who had bled that much one would expect to find rales at the lung bases. We do not know whether he had fever or leukocytosis during the early episodes, though such did occur later on. Evidently the physician doing the examination did not believe that the patient had a chest cold, since it is noted in quotation marks. Pulmonary congestion may well have produced this sensation, for he had had dyspnea on exertion and slight orthopnea. There was little or no evidence of right-sided heart failure during these early attacks except for the slight edema of the legs. There was, however, considerable evidence of pulmonary congestion at the time of his first admission for an episode of hemoptysis,

with no evidence of pulmonary consolidation or of a localized pulmonary lesion.

May we see the x-ray films?

DR. LAURENCE L. ROBBINS: In the first film, taken in the Out Patient Department, there is increased density in the central portion of each lung field. The heart is prominent in the region of the left ventricle, and there is left auricular enlargement. One film shows prominence of the pulmonary artery. I do not see any calcification in either the mediastinum or the aortic valve, but that cannot be determined without fluoroscopy.

This film was taken three years later. The heart has increased in size. In addition there is diffuse increased density centrally located and a fine nodularity scattered through the lung field. Another film taken a year later shows an increase in the nodularity but no change in the central shadow (Fig. 1).

DR. WHEELER: Is the nodularity consistent with that which we see in long-standing mitral disease?

DR. ROBBINS: It is consistent with pulmonary congestion and edema.

DR. WHEELER: There is no evidence of primary pulmonary disease?

DR. ROBBINS: Not that I can see.

DR. WHEELER: The PR interval was still within normal limits. The prominent P<sub>1</sub> and P<sub>2</sub> are in keeping with auricular enlargement. Axis deviation had not developed, showing no preponderance of either ventricle; the patient probably had hypertrophy of both ventricles.

The story at the time of his first admission suggests that the diagnosis of pneumonia, which was entertained, was incorrect. He recovered rapidly and had no x-ray evidence of pulmonary consolidation, and the sputum and blood cultures were negative. A diagnosis of pneumonia is often made in patients with mitral stenosis who present these symptoms.

At the time of his second admission he again had hemoptysis, fever and some leukocytosis, which responded much more quickly to bed rest than is the case with pneumonia or pulmonary infarction.

What happened to the sedimentation rate during the second hospital admission?

DR. RONALD C. SNIFFEN: Only one sedimentation rate is recorded.

DR. WHEELER: Quite a degree of partial auriculoventricular block was present at times, suggesting active rheumatic fever. Again, there was no evidence of pulmonary disease as a cause for the hemoptysis.

The third hospital admission was a repetition of the two preceding entries, and the fourth admission varied only in that the patient failed to recover and apparently died in pulmonary congestion.

This, briefly, then was a patient with rheumatic heart disease with aortic and mitral involvement who suffered from recurrent massive hemoptyses.

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## CLOSING THE RANKS

THE continuance of a democracy is dependent on the ability of its people to hold to their ideals of liberty and to find and follow high leadership. This democracy of ours, changing as it has been with the changing years, undergoing modifications in the pattern of its progress, still youthful enough and great enough to be flexible, has always found great leaders in its periods of crisis.

Emerging safely now from the darkness of our second great national crisis, we have achieved unanimity in the realization of the loss of a great leader. So it was after the death of Lincoln. Constructive, positive leadership cannot exist without

opposition, but under such able guidance as we have had, that opposition is loyal, co-operative and appreciative.

If there is one prayer that we can all join in now, it is that our new president, with the best wishes of his country, will have strength to lead it onward along the path of victory and peace. This he can have only with our full loyalty and support, as we had given them to his predecessor. We must close the ranks and push on.

## PATULIN INEFFECTIVE AGAINST THE COMMON COLD

IN NOVEMBER, 1943, a group of British investigators reported on a new antibiotic agent, patulin, obtained from a strain of *Penicillium patulin*.<sup>1</sup> This substance was considerably more toxic than penicillin but had a wider range of activity and seemed to be effective against gram-negative bacilli. In preliminary clinical trials in uncomplicated cases of the common cold among naval personnel, there appeared to be a definitely higher cure rate after forty-eight hours among persons who sniffed patulin or sprayed their noses and throats with the drug than there was in comparable controls who used a buffer solution without patulin.

These observations were of considerable interest, since common colds constitute a large source of man-days lost, particularly during the early period of training of fresh recruits and among large industries. Because of these favorable results, the director of pathology and the consulting physician to the British War Office sponsored a series of clinical and laboratory trials in military personnel. A report of their findings has recently been published.<sup>2</sup>

Patulin was found to be highly toxic for mice, more so when given subcutaneously or intraperitoneally than when injected intravenously. In rabbits, solutions of patulin, unless extremely dilute, produced local reactions in the cornea and in the skin. Small amounts, injected intra-allantoically, resulted in the death of chick embryos. In therapeutic experiments in mice it was shown to have no effect on influenza A virus infections. In mice treated with patulin and infected with typhoid



largest ulcer was on the noncoronary aortic cusp and measured 1 cm. in diameter. Microscopic sections of these lesions showed an active valvulitis, with endothelial destruction. The character and disposition of the reacting cells within the leaflet were those of rheumatic valvulitis. No bacteria could be found in the overlying thrombus. The right ventricular wall was 9 mm. in thickness, which is about twice the normal size; the left ventricular wall measured 23 mm. There was no increase in pericardial fluid.

There was no pleural fluid, and no ascites. The liver, however, showed chronic passive congestion with a mild central necrosis. The lungs weighed almost 2000 gm. and were dark, firm and meaty. Microscopically they showed the changes that we associate with increased pressure in the pulmonary circulation. They were, however, not so pronounced as those described by Parker and Weiss\* in cases

\*Parker, F., Jr., and Weiss, S. Nature and significance of structural changes in lungs in mitral stenosis. *Am. J. Path.* 12:573-598, 1936.

of severe mitral stenosis. Each alveolar wall showed many more capillary cross-sections than normal, and these capillaries were often dilated to several times the diameter of a red cell. Furthermore, many alveolar walls showed pericapillary edema, which compressed the capillaries. I believe that this is important for, in mitral stenosis, if pericapillary edema is present, gaseous exchange must be hindered. At a later stage in the process some alveolar walls were thickened by a deposit of collagen fibrils, associated with capillary narrowing. In the alveolar spaces there was extensive recent and old hemorrhage, the evidence for the latter being the presence of large numbers of hemosiderin-laden phagocytes. Intra-alveolar edema was slight and scattered. The large and small pulmonary arteries showed sclerosis, but it was not severe.

No Aschoff bodies were found in the myocardium, but unfortunately not enough material was studied to answer the question whether an active myocarditis was present.

The Blue Shield is accomplishing two main objectives: with a service contract for low-income subscribers, it goes farther in the direction of complete protection for serious illness involving surgery than even federal planners and social economists have demanded; and because its policies are controlled and guided by the medical profession itself, the Blue Shield satisfies the demand by doctors that their profession not be dictated to by politicians or outsiders. The reconciliation of these two widely separated aims is difficult. The Blue Shield may properly take pride in the relatively small amount of friction and misunderstanding that have accompanied this complicated task.

Commercial insurance offers cash indemnity, which does not solve the problem for the low-income group. Federal plans, which may aim at satisfying the poor man's need, would accomplish this worthy end through methods that would, in the opinion of most physicians, stultify the medical profession with bureaucracy and federal regulations. The Blue Shield may well be the only possible solution that is tailored both to provide adequate protection for the low-income group and to maintain the highest standards of the medical profession, while preserving the physician's cherished philosophy of freedom of action. It must be reasonably expected that such an enterprise will have its quota of "headaches" and will involve a certain amount of what might be called "postoperative complications."

In 1943 and 1944, Blue Shield payments for surgery, assisting and aftercare, anesthesia and x-rays averaged about \$70 per case. Advisory committees in the various specialties are making continuous progress toward reconciling the differences in opinions regarding certain fees, and in eliminating inconsistencies. Participating physicians are beginning to speak up for the plan, to recommend it for the consideration of influential employers with whom they are acquainted and to distribute Blue Shield pamphlets in their waiting rooms. An average of about five doctors are becoming participating physicians every working day. All this seems to forecast a bright future for the Blue Shield. But, as the December issue of *Fortune* opined in its article "United States Medicine in Transition," if the voluntary or noncompulsory way is to solve the nation's health problem, the following two conditions will have to be met: the country must be prosperous with reasonably full employment, so that people will be able to pay their own contributions without government help; and the government at all levels, employers, the great mass of potential patients and, above all, the medical profession must show a degree of social inventiveness and a determination hitherto unknown.

Physicians cannot afford to be perfectionists in this matter. The Blue Shield is a practical plan, in being, which is becoming more successful each day. It is in a better position now than ever before

to make a new advance toward a better solution. The Blue Shield deserves the united support of the medical profession in Massachusetts.

## DEATHS

BRAY — Thomas A. Bray, M.D., of Holliston, died April 1. He was in his fifty-first year.

Dr. Bray received his degree from Georgetown University School of Medicine, Washington, D. C., in 1922. He maintained a general practice in Worcester six years and then entered the New York Eye and Ear Infirmary, where he studied diseases of the eye, ear, nose and throat two years. He returned to Worcester, practicing his specialty and becoming a member of the staff of St. Vincent Hospital. He moved to Holliston in 1944 and was on the staffs of the Framingham Union and Milford hospitals.

His mother, his widow, three sons, one daughter, a brother and five sisters survive.

CASSELBERRY — Clarence M. Casselberry, M.D., of Newton, died February 25. He was in his seventieth year.

Dr. Casselberry received his degree from the University of Pennsylvania School of Medicine in 1897. He was a fellow of the American Medical Association.

His widow survives.

GOOKIN — Edward R. Gookin, M.D., of Washington, D. C., died recently. He was in his sixty-fourth year.

Dr. Gookin received his degree from Baltimore Medical College in 1906. He was a fellow of the American Medical Association.

A sister survives.

GREENE — Jeremiah A. Greene, M.D., of Cambridge, died April 6. He was in his sixtieth year.

Dr. Greene received his degree from Harvard Medical School in 1913. In 1938 he was appointed associate medical examiner for Middlesex County by Governor Charles F. Hurley. He was a member of the Cambridge Medical Improvement Society and the Massachusetts Medico-Legal Society.

His widow, two sons and two daughters survive.

HOPKINS — William T. Hopkins, M.D., of Lynn, died April 10. He was in his seventy-seventh year.

Dr. Hopkins received his degree from Boston University School of Medicine in 1890. He was formerly Lynn health commissioner. He retired seven years ago after practicing in Lynn for more than fifty years. He was a fellow of the American Medical Association.

His widow, four sons and a brother survive.

NOYES — Nathaniel K. Noyes, M.D., of Plymouth, died April 12. He was in his eighty-first year.

Dr. Noyes received his degree from Dartmouth Medical School in 1890. During World War I, he was a captain in the Army Medical Corps. He was health-board physician in Duxbury from 1895 to 1925. He served as visiting physician at the Jordan Hospital, Plymouth, from 1915 to 1925 and as associate medical examiner of the Third Plymouth District for three terms. He was a fellow of the American Medical Association and a member of the Massachusetts Association of Health Boards and the Massachusetts Medico-Legal Society.

His widow, a son, two daughters and a brother survive.

YOUNG — Edward L. Young, III, M.D., of Brookline, was killed in action on March 24 in Germany. He was in his thirty-first year.

Dr. Young received his degree from Harvard Medical School in 1941. He entered the service in May, 1943, after serving his internship at the Massachusetts General Hospital. He went overseas in March, 1944, and was serving at a field hospital in the front lines.

His father, his widow, a daughter and a sister survive.

bacilli the death rate was higher during the first two days after injection than in controls that received no patulin. The controlled clinical trials in the treatment of the common cold with patulin showed no advantage from its use as compared with that of a buffer solution without patulin.

These investigators emphasized the great difficulty in assessing the effect of any treatment in the common cold in view of the lack of objective signs that can serve as a check on subjective findings. They attempted to eliminate bias during treatment and in evaluating the results. Neither the investigators nor the patients knew which type of treatment was used, patulin or control. All the results were obtained before an analysis was attempted. The main trial was carried out in 100 men at a recruiting establishment during the season of autumn colds. Half the men were treated with patulin, and the others with the control buffer solution that served as the vehicle for the patulin. The two groups were comparable with respect to age, severity of symptoms, duration before and after treatment and bacteriologic findings. No dramatic effects were observed in either group. The patulin solutions used in the final trials were tested for bacteriostatic action nine weeks after their preparation and after the trials had been concluded. They retained their full activity as compared with fresh solutions. It was concluded that patulin had no demonstrable effect on the course of this series of colds.

When the preliminary results of these trials became known, the British Medical Research Council undertook an extensive investigation of the contradictory claims.<sup>3</sup> A study was carried out in several large factories and post-office units widely scattered throughout England. In these studies the test solutions were used as nose drops, but in two additional trials in public schools the solutions were also used as sprays. These clinical trials were supervised by local medical officers, and all the subjects were volunteers. Attempts were made to exclude cases of hay fever and chronic respiratory disease, and a uniform record system was used. In order to reduce the chances of guessing, four different solutions were used in each establishment, two of them containing patulin and the other two containing

only the buffer solution. The solutions were freshly made, being used before they were three days old. The results in 1348 cases were available for analysis. Of these, 668 were treated with patulin, and 680 with control solutions. No significant differences were found among the separate units. There was an almost identical percentage of cures at different intervals after the treatment was begun in those who received patulin and in those who were given the control buffer solution. This was true irrespective of the duration of illness at the time when treatment was started. From these studies, therefore, no evidence was found to indicate that patulin is effective in the treatment of the common cold.

It is only fair to point out that these results were obtained with a substance that is relatively toxic when applied locally. It may still be possible that other antibiotics that are both more effective against bacterial infections and more innocuous to tissues will prove helpful in the treatment of the common cold and reduce the chances for the establishment of secondary bacterial complications. On the whole, however, most of the experiences thus far with the topical use of sulfonamides or penicillin in mixed infections have not been too encouraging.

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#### MASSACHUSETTS MEDICAL SOCIETY



The Blue Shield, now in its twenty-seventh month of operation, is beginning to make significant gains. The plan has added more new members in the past six months than it acquired in the first eighteen months of business. With nearly 125,000 members and 4000 participating physicians, it would seem that the Blue Shield has established itself as a definite part of the medicoeconomic structure.

Perceiving that the Doctor had no disrelish for my freedom, I ventured a step further, and said: "Doctor, there have been and still are among the people, especially among the more ignorant, many fanciful conceits and absurd notions received by time-honored tradition and confidently relied on as helps or hindrances to a cure, and sometimes a wise prescription might contradict the delusion and disturb, if not destroy the confidence of the patient in the skill of his physician. How far may such delusions be honestly humored? How would you avoid disturbing the patient's confidence?"

The wary Doctor was at no loss for a reply, and ignoring all metaphysics, proceeded at once to illustrate the matter by relating an occurrence in his own early practice. I wish I could tell you the story just as he told it to me, but you know how impossible it is to put on paper flexible tones and looks, so often the very soul of utterance. However, you knew the Doctor too long and intimately not to remember well the imposing gravity he could assume in relating what was either facetious or ridiculous. The story as nearly as I can give it in lonesome black and white is the following:

Not long after I began to practice medicine in Leicester, a well-meaning man, the owner of a few acres and little or nothing else, called on me early in the spring of the year for professional relief. He complained in a forlorn way that he was ailing and felt very weak. He said he was afraid he should not be able to do his spring work himself, and that he was too poor to hire anybody to do it for him. With a pitiful look he desired me to do something for him if possible, that he might get better and be able to go to work in season for planting time. After a little examination and a few inquiries I thought I saw his case, and directed him to get some wild cherrytree bark, make a decoction of it, and take so much, so often daily in spirit. He listened intently to all I said, and when I ended my prescription he said with a look of eager honesty, "Doctor, shall I strip the bark up or down?" the belief being then, and having long been common, that if the bark was stripped up from the tree, the medicine would work up, and if stripped down, it would work down. I replied, "In your complaint it is not of the least importance whatever whether you strip it up or down but don't you strip it sideways for the world!! If you do it will work right between your ribs!" The poor man cheered up, got better, did his spring work, and in due season gathered in the fruits of his own honest labor.

## BOOK REVIEWS

*Artificial Pneumothorax in Pulmonary Tuberculosis: Including its relationship to the broader aspects of collapse therapy.* By F. N. Rafferty, M.D. With an introduction by Henry S. Willis, M.D. 8°, cloth, 192 pp., with 26 illustrations and 14 tables. New York: Grune and Stratton, 1944. \$4.00.

Artificial pneumothorax therapy for pulmonary tuberculosis came during the early twenties of this century like a gust of fresh air on a hot and parched summer's afternoon. For years, the world had been waiting hopefully for that elusive cure of the then greatest killer of men — pulmonary tuberculosis. In a period of a few years, it was hailed as an important advance in the control and alleviation of tuberculosis, and the acceptance of this form of therapy was greatly hastened because of the simplicity of administering it and the fact that all sanatoriums could make full use of it. Gradually, however, complications began to ensue and late results came to plague both the physician and the patient, and recently certain authorities have criticized this method of treatment. Thus, many phthisiologists became bewildered and did not know where to turn. It is therefore doubly welcome that Dr. Rafferty has penned this book and has shown them a way out.

In the eighteen chapters, the author has included not only his own experiences but also those of all the major clinics in this country. He knows the limitations of pneumothorax therapy but also understands its benefits. First, he is of the opinion that primary thoracoplasty has its place and should not necessarily follow pneumothorax therapy. He deprecates the use of pneumothorax therapy in extensive disease, in apical cavities and in bronchial involvement. He urges a trial of pneumothorax therapy for a few weeks and its aban-

donment if unsuccessful, especially if many adhesions prevent relaxation of the lung and pneumonolysis is not feasible. He is particularly emphatic on early re-expansion in cases of empyema and bronchial fistula. His discussion on tension cavity is scholarly. He has purposely left out many of the small details, and he deals more with effective and ineffective pneumothorax therapy, pneumothorax with phrenic paralysis, the prevention of complications and so forth.

This small book is written in an excellent style and should be read by all interested in the treatment of pulmonary tuberculosis.

*Secretory Mechanism of the Digestive Glands.* By B. P. Babkin, M.D., D.Sc., LL.D. 8°, cloth, 900 pp., with 220 illustrations. New York: Paul B. Hoeber, Incorporated, 1944. \$12.75.

Dr. Babkin, who is research professor of physiology at McGill University, Montreal, and former professor of physiology at the University of Odessa, has written a valuable, up-to-date account of the experimental analysis of the secretory function of the digestive glands in carnivorous animals and man. The author writes easily and clearly. Throughout the book he rightly emphasizes the fact that it is only by a combined morphologic and physiologic approach that an understanding of the complicated phenomena of bodily function can be reached. Theories are interestingly presented but merely to serve as guides to facilitate further progress of the problems discussed. The mechanisms involved in the regulation of the secretory activity of the principal digestive glands are critically reviewed historically and then brought to the point where the author indicates the problems that await further investigation. An excellent bibliography covers eighty-five pages, and there is a good index.

This book should serve well the clinician who is charged with the clear understanding and the investigation of the diseases of the secretory apparatus of the alimentary canal.

*The Radiology of Bones and Joints.* By James F. Brailsford, M.D., Ph.D., F.R.C.P., F.I.C.S. Third edition. 8°, cloth. 440 pp., with 404 illustrations. Baltimore: Williams and Wilkins Company, 1944. \$12.00.

In the third edition of this important roentgenologic treatise the author has attempted to add new information and "bridge the gaps" that were present in previous editions. The four years of war have added to the author's difficulties in gathering data concerning patients. In spite of the difficulties, a most creditable volume has been published. The only adverse change is a poorer grade of paper and a more condensed arrangement of the printed material. The roentgenologic discussion is divided according to anatomic location. This is probably as good a division as can be made considering the varied nature of the lesions described, but it occasionally makes dull reading. The varied picture of injury and disease shown in x-ray films is fully described. There are many helpful sketches, as well as numerous excellent photographs of the roentgenograms. A number of excellent teaching outlines list the diseases that frequently produce a certain type of change in bones in the various areas of the body. There are many references to the recent orthopedic literature.

This book represents twenty-five years of experience of one of the leading roentgenologists of England, and it can be recommended as an authoritative treatise on the roentgenologic aspects of lesions of the bones and joints. It should prove to be a most helpful reference book for both roentgenologists and orthopedic surgeons.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Foundations of Neuropsychiatry.* By Stanley Cobb, M.D., Bullard Professor of Neuropathology, Harvard Medical School, and psychiatrist-in-chief, Massachusetts General Hospital. Third edition, revised and enlarged, of the work

# MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

## COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MARCH, 1945

### RÉSUMÉ

DISEASES	MARCH 1945	MARCH 1944	SEVEN-YEAR MEDIAN
Anterior poliomyelitis.....	5	0	0
Chancroid.....	4	2	0
Chicken pox.....	1319	3360	1604
Diphtheria.....	22	25	14
Dog bite.....	783	733	733
Dysentery, bacillary.....	4	19	4
German measles.....	225	316	147
Gonorrhea.....	459	509	327
Granuloma inguinale.....	1	0	*
Lymphogranuloma venereum.....	2	5	*
Malaria.....	76	55	0
Measles.....	624	3546	3245
Meningitis, meningococcal.....	22	60	10
Meningitis, Pfeiffer-bacillus.....	1	4	2
Meningitis, pneumococcal.....	5	7	†
Meningitis, staphylococcal.....	0	0	†
Meningitis, streptococcal.....	0	1	†
Meningitis, other forms.....	0	0	†
Meningitis, undetermined.....	3	20	†
Mumps.....	2790	1575	1303
Pneumonia, lobar.....	257	424	516
Salmonella infections.....	8	12	3
Scarlet fever.....	1701	1906	1457
Syphilis.....	412	674	479
Tuberculosis, pulmonary.....	239	228	283
Tuberculosis, other forms.....	20	21	21
Typhoid fever.....	1	2	3
Undulant fever.....	5	3	3
Whooping cough.....	854	376	874

\*Made reportable December, 1943.

†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

### COMMENT

Anterior poliomyelitis thus far this year has been at the highest point since 1932. The March total exceeded any since 1928.

Diphtheria, although well above the seven-year median, is running lower this year than last.

Meningococcal meningitis during the first quarter of 1945 was consistently below that of the corresponding three months of the last two years.

None of the relatively large number of cases of malaria reported in March originated in Massachusetts. They occurred in returned members of the armed forces.

### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Cambridge, 1; Framingham, 1; Longmeadow, 1; Lynn, 1; Springfield, 1; total, 5.

Diphtheria was reported from: Boston, 3; Cambridge, 2; Framingham, 1; Hanson, 1; Lowell, 4; New Bedford, 2; Reading, 1; Somerville, 2; Taunton, 3; Wareham, 1; Winchester, 1; Worcester, 1; total, 22.

Dysentery, amebic, was reported from: Waltham Regional Hospital, 1; total, 1.

Dysentery, bacillary, was reported from: Boston, 1; Lawrence, 2; Northampton, 1; total, 4.

Encephalitis, infectious, was reported from: Brockton, 1; Chelmsford, 1; Everett, 1; Lexington, 1; Medford, 1; Quincy, 1; Weymouth, 1; total, 7.

Malaria was reported from: Boston, 1; Camp Edwards, 43; Cushing General Hospital, 11; Haverhill, 1; Lynn, 1; Melrose, 1; Natick, 1; Northampton, 2; Norwood, 1; Waltham Regional Hospital, 11; Waltham, 1; Winchester, 1; Worcester, 1; total, 76.

Meningitis, meningococcal, was reported from: Beverly, 1; Boston, 6; Chelmsford, 1; Fall River, 2; Fitchburg, 1; Holyoke, 1; Milton, 1; New Bedford, 1; Newton, 1; Palmer, 1; Plymouth, 1; Quincy, 1; Southboro, 1; Worcester, 3; total, 22.

Meningitis, Pfeiffer-bacillus, was reported from: Milford, 1; total, 1.

Meningitis, pneumococcal, was reported from: Amherst, 1; Lawrence, 1; Springfield, 1; Worcester, 2; total, 5.

Meningitis, undetermined, was reported from: Brockton, 1; Cambridge, 1; Springfield, 1; total, 3.

Salmonella infections were reported from: Beverly, 1; Boston, 1; Lynn, 1; Natick, 3; Revere, 2; total, 8.

Septic sore throat was reported from: Amesbury, 1; Arlington, 1; Boston, 9; Cambridge, 1; Fall River, 1; Lowell, 1; Medford, 1; Newton, 1; Quincy, 1; Salem, 1; Williamstown, 2; total, 20.

Trichinosis was reported from: Boston, 1; Douglas, 1; Haverhill, 1; Millbury, 1; Norton, 1; West Stockbridge, 2; total, 7.

Typhoid fever was reported from: Adams, 1; total, 1.

Undulant fever was reported from: Brookfield, 1; Northampton, 1; Northbridge, 1; Raynham, 1; Worcester, 1; total, 5.

## CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	May 2	William T. Green
Lowell	May 4	Albert H. Brewster
Salem	May 7	Paul W. Hugenberger
Brockton	May 10	George W. VanGorder
Springfield	May 16	Garry deN. Hough, Jr.
Worcester	May 18	John W. O'Meara
Pittsfield	May 21	Frank A. Slowick
Hyannis	May 22	Paul L. Norton
Fall River	May 28	Eugene A. McCarthy

## MISCELLANY

### NOTE

Dr. Derek Denny-Brown, professor of neurology at Harvard Medical School and director of the Neurological Unit, Boston City Hospital, has been granted leave of absence by these institutions. He is to return to active military duty as a brigadier general with the British forces in India and South East Asia. In 1941, after two years of service in the field, he was temporarily released by the British Army to carry on research and teaching in the United States. He plans to resume his work in Boston at some later date.

## CORRESPONDENCE

### SPRING TONIC

To the Editor: The following anecdote written by the aged Rev. George Allen for Joseph A. Denny, of Leicester, Massachusetts, has recently come into my possession.

The Austin Flint referred to may have been a connection or even an ancestor of the two famous Austin Flints.

A. E. P. ROCKWELL, M.D.

Shrewsbury, Massachusetts

\* \* \*

Joseph A. Denny, Esq.

Dear Sir:

Herewith I send the promised trifle. I prepared it soon after I last saw you, but knowing that if used at all, other matter must take precedence, I lay it aside to meet other calls of immediate claim; and you know out of sight is out of mind for some, especially an old man.

If you cannot decipher or guess at my hieroglyphics, perhaps I can tell what I meant, should you deem it important enough to trouble yourself about it.

Respectfully yours,

GEORGE ALLEN

Jan. 16, '74

\* \* \*

In conversation with the late Doctor Austin Flint when he was not far from his ninetieth year, I remarked to him that he had passed almost the whole of his professional life in Leicester, and had had many and special opportunities for learning the ways and sentiments of all classes of the people. To these remarks the Doctor of course assented.

I next intimated with respectful deference my opinion that a patient's faith in the skill and practice of his physician is sometimes an effective auxiliary to mere medical treatment. To this he replied, "It is so in cases not a few."

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## PANCREATODUODENAL RESECTION\*

### A Preliminary Report of Eighteen Cases

RICHARD B. CATTELL, M.D.†

BOSTON

DURING the past decade a new field in abdominal surgery has been explored with the successful removal of the duodenum and pancreas for malignant tumors by a radical block pancreatoduodenal resection. Previously, all attempts to remove carcinomas in this area had been confined to local excisions of malignant tumors of the duodenum or ampulla of Vater, which, in the light of the present knowledge, could be considered little more than palliative resections, with a small chance for complete extirpation of the tumor. Furthermore, these excisions were frequently followed by serious complications, such as retroperitoneal sepsis, external and internal fistulas and strictures of the common bile duct and pancreatic duct. The radical removal of tumors at other sites, such as carcinomas of the breast, stomach, colon and rectum and uterus, has been proved conclusively to give the best results. If it can be demonstrated that the block type of resection (pancreatoduodenal resection) for malignant tumors in this region can be feasibly done with few complications and a low operative mortality, it may then be accepted and more widely applied. Experiences at the Lahey Clinic with 18 resections of this type are presented in the hope of furthering interest in these cases, which are usually considered hopeless.

#### HISTORY

Although Halsted<sup>1</sup> performed a local excision of carcinoma of the ampulla as early as 1898, and Mayo<sup>2</sup> resected a hyperfunctioning carcinoma of the pancreas in 1927, it remained for Whipple,<sup>3</sup> in 1935, to focus interest on these cases when he and his associates reported a successful resection. Since that time Hunt<sup>4</sup> has reported 4 cases, with a review of the literature, including both local and radical operations, Trimble<sup>5</sup> has reported a successful one-

stage operation, and Harvey and Oughterson<sup>6</sup> have reported 6 cases, not all of them radical. More recent reports by Brunschwig<sup>7</sup> and Gray<sup>8</sup> and previous reports by me<sup>9-11</sup> indicate a growing interest in the field. Approximately 100 operations that could be termed radical in the usual sense applied to the surgical treatment of malignant tumors have been performed.

#### GENERAL CONSIDERATIONS

From our experiences with these cases, approximately 30 per cent of malignant tumors causing jaundice as a primary symptom are suitable for resection. One of the most difficult problems in the management of such cases is that of establishing the diagnosis at operation when it has been suspected preoperatively. The clinical course of carcinoma of the pancreas and carcinoma of the ampulla is quite similar. As shown by Kiefer,<sup>12,13</sup> the development of symptoms associated with carcinoma of the pancreas is slow, with jaundice developing somewhat late, with weight loss, anemia and cachexia appearing first. We have found that in patients with carcinoma of the ampulla, jaundice is the presenting symptom, with the general systemic effects following. Unless a palpable mass is present, the time of development of jaundice is the only clinical means of differentiating these two conditions. In the past the diagnosis of carcinoma of the pancreas has been made in all cases of painless jaundice, irrespective of the order of the development of the symptoms. In our experience, carcinoma of the ampulla is more frequent than carcinoma of the pancreas. Since jaundice develops late with cancer of the pancreas, many of these cases are unsuitable for resection, since metastases or local spread makes it impossible. The degree of malignancy is high in cancer of the pancreas and low in cancer of the ampulla, and it is our experience that most carcinomas of the ampulla are suitable for resection.

\*Presented at the annual meeting of the New England Surgical Society, Boston, September 20, 1944.  
†From the Department of Surgery, Lahey Clinic.  
‡Surgeon, Lahey Clinic.

formerly known as *A Preface to Nervous Disease*. 8°, cloth, 252 pp., with 13 illustrations and 3 tables. Baltimore: Williams and Wilkins Company, 1944. \$2.50.

This standard text has been revised and enlarged to bring it into line with recent advances in the field of neuropsychiatry. New knowledge in the experimental field hitherto confined to animals has been tested on human beings with success. A new chapter has been added dealing with the psychopathologic concepts that are important in medicine.

*The Trials and Triumphs of the Surgeon, and Other Literary Gems*. By J. Chalmers Da Costa, M.D., LL.D. Edited by Frederick E. Keller, M.D. 8°, cloth, 401 pp. Philadelphia: Dorrance and Company, 1944. \$5.00.

Here for the first time are collected the minor writings of Dr. Da Costa, who was the Samuel D. Gross Professor of Surgery at Jefferson Medical College of Philadelphia from 1910 to 1930. The papers are mostly historical.

*Gynecological and Obstetrical Urology*. By Houston S. Everett, M.D., associate professor of gynecology, Johns Hopkins University, associate in gynecology, University of Maryland, assistant visiting gynecologist and gynecologist in charge of the Cystoscopic Clinic, Johns Hopkins Hospital, and visiting gynecologist, Church Home and Hospital, Hospital for the Women of Maryland and Union Memorial Hospital. 8°, cloth, 517 pp., with 220 illustrations. Baltimore: Williams and Wilkins Company, 1944. \$6.00.

This new textbook is based on the author's ten years' experience in the teaching of urology in the Department of Urology of Johns Hopkins University Medical School. It has been written for medical students, general practitioners, gynecologists and obstetricians, who may be confronted with urologic problems in their practice. Particular stress has been made on the general nature of urologic disease and its relation to general medicine and the other specialties.

*A Textbook of Pathology: Pathologic anatomy in its relation to the causes, pathogenesis and clinical manifestations of disease*. By Robert A. Moore, M.D., Edward Mallinckrodt Professor of Pathology, Washington University School of Medicine, Saint Louis. 8°, cloth, 1338 pp., with 513 illustrations. Philadelphia and London: W. B. Saunders Company, 1944. \$10.00.

This new textbook on pathology embodies a new departure in classification in which degeneration is approached by disturbances of metabolism rather than by anatomic types. In the section on special pathology, diseases with similar causes have been grouped together; and those diseases of which the causes are unknown or obscure have been considered according to the organ or the system in which they occur. Bacterial diseases have been classified according to the portal through which the bacterium enters the body and the source of bacterium. The work is well printed on good paper with a good type and copiously illustrated. There are extensive citations to the literature scattered throughout the text.

*Taber's Dictionary of Gynecology and Obstetrics*. By Clarence W. Taber, with the collaboration of Mario A. Castallo, M.D., assistant professor of obstetrics, Jefferson Medical College, gynecologist to St. Mary's and St. Agnes hospitals and obstetrician to St. Mary's Hospital. 16°, cloth, 700 pp., with illustrations. Philadelphia: F. A. Davis Company, 1944. \$3.50.

This is a specialized medical dictionary designed for all those interested in gynecology and obstetrics. No attempt has been made to supply a general vocabulary, but the selection of words has been limited to those dealing with the two principal subjects. Many of the definitions are encyclopedic in character, and some of the subjects are treated at considerable length. The unusual method of numbering the pages by sections, such as A-51, O-17, and so forth, is confusing and does not seem to possess any particular advantage over the usual system. The long section on the common infectious diseases of infancy and the emergencies in infancy and childhood seem to be out of place in this particular work.

*Neurology of the Eye, Ear, Nose and Throat*. By E. A. Spiegel, M.D., professor of experimental and applied neurology and head of the Department of Experimental Neurology, Temple

University School of Medicine; and I. Sommer, M.D., lecturer in ophthalmology, Long Island College of Medicine, and consultant ophthalmologist and otolaryngologist, Chicago Eye and Ear Hospital. 8°, cloth, 667 pp., with 118 illustrations. New York: Grune and Stratton, Incorporated, 1944. \$7.50.

This book is intended to cover the borderland between the field of neurology and the fields of otolaryngology and ophthalmology. The text is based on postgraduate lectures given within the last twenty-five years at the University of Vienna and at Temple University. The present publication has been based partly on the 1931 Berlin edition but has been completely rewritten. A bibliography of 1719 selected references is appended to the text. The book is well printed on good paper, with a good sight-saving type.

*The Diagnosis and Treatment of Acute Medical Disorders*. By Francis D. Murphy, M.D., professor of medicine and head of the department of medicine, Marquette University School of Medicine, and clinical director of the Milwaukee County General Hospital and Emergency Unit, Milwaukee. 8°, cloth, 503 pp., with illustrations. Philadelphia: F. A. Davis Company, 1944. \$6.00.

This book is intended for the general practitioner and the medical student and is based on an experience of more than twenty years at the Milwaukee County General Hospital.

*Operations of General Surgery*. By Thomas G. Orr, M.D., professor of surgery, University of Kansas School of Medicine, Kansas City, Kansas. 4°, cloth, 723 pp., with 1396 illustrations. Philadelphia: W. B. Saunders Company, 1944. \$10.00.

In this new text on general operative surgery, illustrations have been emphasized and the text has been purposely made as brief as is consistent with a step-by-step description of each operation. The chapters have been arranged, in so far as possible, according to the systems of the body or under special headings, such as plastic and neurologic surgery, urology and gynecology. Chapters on wound healing and on the treatment of fresh wounds have been included.

## NOTICES

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 10

- FRIDAY, MAY 11**  
 \*9:00-10:00 a.m. Carcinoma of the Prostate. Dr. William C. Quimby. Joseph H. Pratt Diagnostic Hospital.  
 \*9:00-10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.  
 10:50 a.m. X-ray Diagnosis of Syphilis. Dr. Max Ritvo. (Post-graduate clinic in dermatology and syphilology.) Amphitheater, Mallory Building, Boston City Hospital.  
 12:00 m.-1:00 p.m. Clinicopathological conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
- SATURDAY, MAY 12**  
 \*10:00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.
- MONDAY, MAY 14**  
 \*12:00 m.-1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.
- TUESDAY, MAY 15**  
 \*9:00-10:00 a.m. Clinicopathological conference. Drs. Chester S. Keefer and H. F. MacMahon. Joseph H. Pratt Diagnostic Hospital.  
 \*9:00-10:00 a.m. Medical clinic. Infants' Hospital.  
 \*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
- WEDNESDAY, MAY 16**  
 \*9:00-10:00 a.m. Endocrine Problems in Childhood. Dr. Richard Wagner. Joseph H. Pratt Diagnostic Hospital.  
 \*12:00 m. Clinicopathological conference. Children's Hospital.

\*Open to the medical profession.

(Notices continued on page xvii)

the gastrointestinal or the biliary tract. Extension of the tumor makes resection inadvisable. If the superior mesenteric vessels are found to be involved and cannot be freed, this can be determined early in the dissection. If these are freed, the portal vein is then exposed and a finger is placed under the neck of the pancreas to be sure that it can be detached. If the case is deemed inoperable, some benefit may follow ligation of the gastroduodenal artery and inferior pancreaticoduodenal artery in continuity. In a patient with complete obstruction of the duct of Wirsung we were able to do a side-to-side anastomosis in continuity between the dilated duct

creatoduodenal area should be avoided if possible in this stage. I recommend that a cholecystjejunostomy be done 30 to 45 cm. from the ligament of Treitz, and accompanied by jejunojejunostomy 15 or 20 cm. proximal to the cholecystjejunostomy. The enteroenterostomy defunctionalizes the loop of jejunum used for the biliary anastomosis, and at the second stage the pancreatojejunal anastomosis can be made in the afferent loop distal to the jejunojejunostomy. This biliary anastomosis is simple to perform, and if the omentum is drawn down over it the field for the pancreaticoduodenal resection will be uncomplicated by adhesions at the second stage.

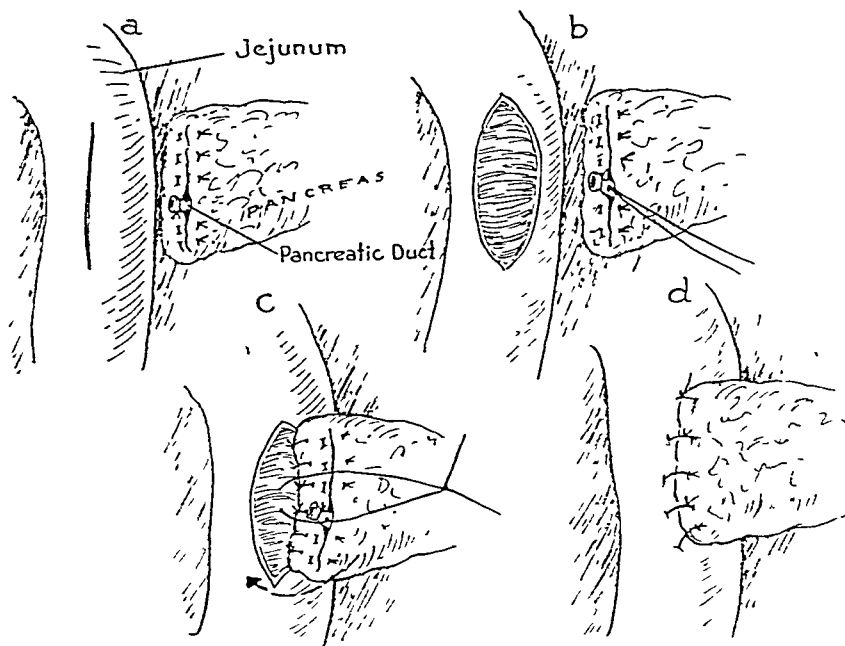


FIGURE 2. *A Technical Method of Avoiding External Pancreatic Fistula.*

a — the serosal and muscular layers of the jejunum have been incised, the incised pancreas has been closed, and the pancreatic duct has been ligated; b — the serosa and muscularis have been spread, and the pancreatic duct has been transfixed by a silk suture; c — the posterior surface of the pancreas has been joined to the lateral wall of the jejunum, and the transfixing silk suture now transfixes the mucosa of the jejunum; and d — the pancreatojejunal anastomosis is completed by the anterior suture line. (Reproduced from Cattell<sup>9</sup> with permission of the publisher.)

and the jejunum, with considerable temporary improvement in the patient's condition.

There is as yet no unanimity of opinion relative to the employment of the one-stage versus the two-stage operation for these cases. In my opinion, the two-stage operation should be employed if jaundice is severe, with the bilirubin over 5 mg. per 100 cc., if the liver function is shown to be low by liver-function tests or if the patient's general condition is poor. Since jaundice is usually the presenting symptom, many of these cases can be done in two stages with less risk. If the two-stage operation is chosen, the first stage should consist solely of an anastomosis of the biliary tract to the intestine. Any exploration of the common duct or of the pan-

There is little question that the patient will be much improved after the first stage and that a definite lowering of operative risk will result. The magnitude of the second stage is little affected by the first-stage operation, since the only difference between the second stage and the one-stage resection is that the common duct is closed off rather than used as a choledochojejunostomy.

#### TECHNIC

The technic of pancreaticoduodenal resection will not be presented in this paper, but the order of procedure will be briefly summarized.

The duodenum and pancreas are elevated by division of the peritoneum, carrying the dissection



There may be considerable difficulty in proving the presence of cancer at the time of operation. Biopsies of the pancreas when taken as deeply as possible from a pancreatic mass obviously cancerous are frequently negative. Tumors of the ampulla are usually small, being 1 to 2 cm. in diameter even three to six months after they have produced obstruction of the common bile duct, and are difficult to palpate through the head of the pancreas or duodenum. The head of the pancreas frequently has extensions and divisions, due to its racemose character, that on palpation may be confused with tumor. We have explored 3 cases at a second stage, in which a tumor was palpated at the first stage, without finding a tumor, and one resection carried out in a fourth patient with a palpable tumor but cancer could not be demonstrated microscopically. It is important to emphasize the difficulties of establishing the diagnosis at operation, and it is necessary in many cases to do the radical operation without the benefit of a positive biopsy. If cancer is shown by biopsy to be present in the gastrohepatic or gastrocolic ligaments, the radical operation may not be justified. A positive diagnosis can be established by transduodenal exploration of the ampulla, since cancerous tissue can readily be procured. Dilatation of the common duct has been present in all our cases in which cancer was proved. The 3 patients who had an exploratory second stage with the possibility of resection did not have dilated common ducts. In cases in which malignancy cannot be proved, unless dilatation of the common duct is present, resection should not be done. It has been our experience in patients with carcinoma of the ampulla that biopsy is unnecessary, since the projecting tumor can usually be palpated through the duodenal wall.

#### GENERAL OPERATIVE PLAN

Pancreatoduodenal resection is a formidable operative procedure (Fig. 1) that is time-consuming and difficult, and good operating conditions are essential. We prefer fractional spinal anesthesia, using pontocaine weighted with glucose, with 40 to 50 mg. of the drug in divided doses of 15, 10, 10 and 10 mg., since the operation may take two and a half to four and a half hours. Two transfusions are usually given during the procedure.

The major operative problems are the control of the blood supply as it enters the general field by ligating large vessels and the interruption and restoration of continuity of the gastrointestinal tract, the biliary tract and the pancreas. In the earlier reported cases it was considered unnecessary to restore the pancreatic juice to the intestine, and several successful cases were reported in which no external pancreatic fistula developed and no spontaneous internal fistula could be proved, and in which good health was maintained in spite of its loss. It is our opinion, however, that many of the

complications following pancreatoduodenal resection are related to internal or external pancreatic fistulas in spite of ligation of the pancreas and its duct.

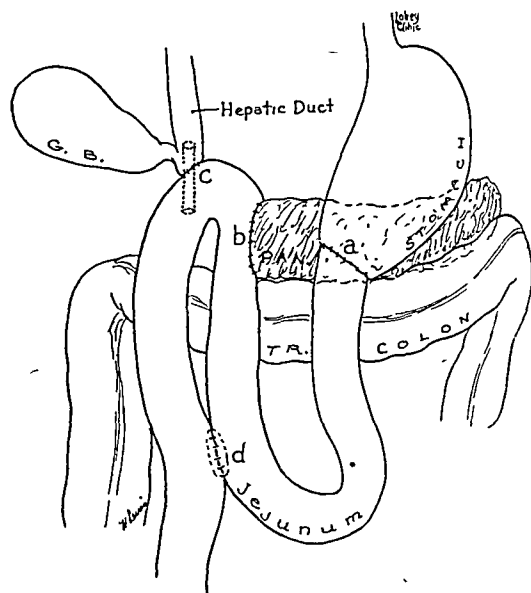


FIGURE 1. The Completed One-Stage Pancreatoduodenal Resection.

All anastomoses are antecolic. a — end-to-end gastroduodenal anastomosis; b — end-to-side pancreatoduodenal anastomosis; c — end-to-side choledochoduodenal anastomosis; and d — jejunoduodenal anastomosis. (Reproduced from Cattell<sup>1</sup> with permission of the publisher.)

This was true in our first case, in which digestion of the stump of the gastroduodenal artery resulted in hemorrhage. Similarly, a longer convalescence may result and retroperitoneal sepsis is likelier to follow. I have previously described a technic of anastomosis of the duct of Wirsung to the jejunum to avoid pancreatic fistula (Fig. 2). The re-establishment of the biliary tract is not difficult, and in the one-stage operation the common duct is anastomosed to the jejunum, whereas in the two-stage operation a cholecystjejunostomy is performed at the first stage. The third or fourth portion of the duodenum has been reported as used for both the pancreatic and biliary anastomoses, but we have utilized a long loop of jejunum for this purpose. It is preferable to use a defunctionalized loop of jejunum, which can be accomplished by side-to-side jejunojejunostomy or by utilizing the Roux principle as described by Whipple.<sup>3</sup> Jejunojejunostomy is unnecessary if the stomach is joined to the efferent jejunum below the pancreatic and biliary anastomoses.

#### OPERATION

The first step of operation is to establish the diagnosis by the means outlined earlier in this paper, following which operability is determined. If the patient's condition justifies a one-stage operation, a dissection of the entire field can be carried out with good mobilization without dividing either

ampulla. In addition, 3 patients were explored at the second stage; after freeing of the pancreas no tumor was found, and the operation was discontinued.

The first patient was operated on in August, 1939, and the remainder have been operated on since August, 1942. During the two-year period from August, 1942, to August, 1944, 51 patients with carcinoma of the pancreatoduodenal region have been observed, with 24 having no operation or having exploration, drainage of the common duct or cholecystjejunostomy performed for palliation only.

was found. Weight loss was a conspicuous symptom, with only 2 patients having none. The average weight loss was 20 pounds, and 1 patient lost 42 pounds in six months. Anorexia, weakness, malaise, diarrhea, mushy stools, pruritus and indigestion were frequent later symptoms. One patient had severe epigastric pain, with deep jaundice, but at the time of operation was found to have gallstones and carcinoma of the ampulla.

The laboratory findings were similar to those of other abdominal cancers. The blood bilirubin was consistently elevated, varying from 1.6 to 21.4 mg.

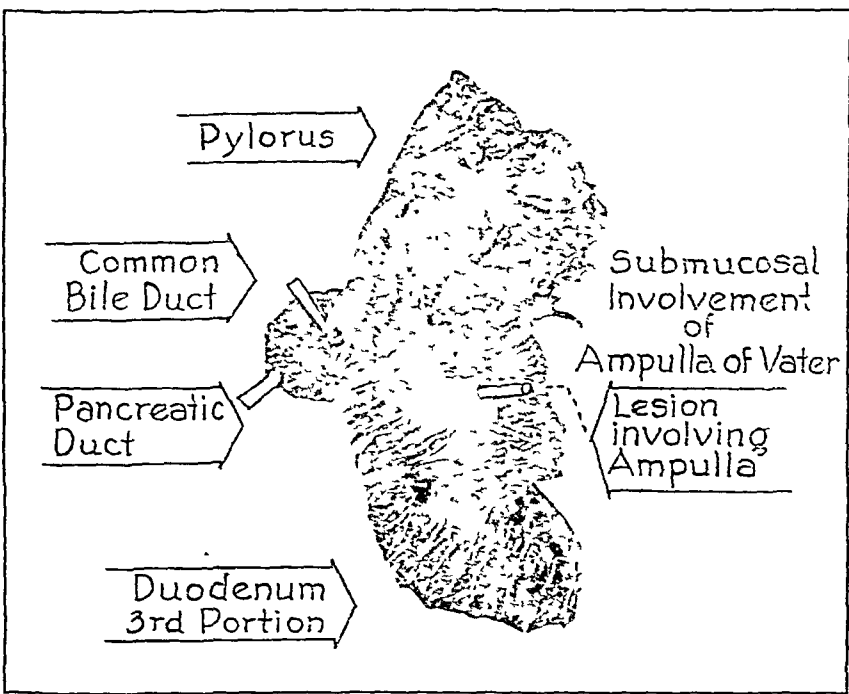


FIGURE 4. *The Mucosal Surface of a Pancreatoduodenal Resection. The circumscribed adenocarcinoma projects through the duodenal wall.*

Seventeen patients were submitted to radical resection during this period, and in an additional 10 the second stage was planned but not done.

Comprising these 18 cases in which operation was performed, there were 13 men and 5 women. Two patients were between forty and forty-nine years old, 8 between fifty and fifty-nine, 6 between sixty and sixty-nine, and 2 over seventy. One of the patients explored at the second stage with no tumor being found was only twenty-seven years of age, with the age incidence in this series cancer seems unlikely to occur at such an early age.

Four patients had had symptoms for less than one month, 6 for one to three months, 4 for three to six months, and 1 for six to twelve months. Three had had symptoms for over a year.

The presenting symptom in 16 cases was jaundice, and in 2 other patients anemia of unexplained origin

per 100 cc. The 2 patients without clinical jaundice had a bilirubin of 1.6 and 1.9 mg., respectively. The prothrombin time was little affected

*Preoperative Diagnosis*

The diagnosis of stones in the common duct was made in 4 cases, cancer of the stomach in 1, retroperitoneal sarcoma in 1, in which there was no jaundice, and cirrhosis of the liver in 1. Six patients were operated on with a diagnosis of carcinoma of the pancreas, and a diagnosis of carcinoma of the ampulla was made in 8. Two diagnoses were made in 3 cases, so that twenty-one diagnoses are listed for the 18 cases. Common-duct stone and cancer of the pancreas were diagnosed in 1 case, carcinoma of the ampulla and cirrhosis of the liver in 1, and common-duct stone and carcinoma of the ampulla in 1.

under the superior mesenteric vessels. The two anterior layers of the gastroduodenal omentum are then divided, freeing the distal third of the greater curvature of the stomach. The gastrohepatic ligament is next divided, with ligation of the right gastric artery. Following this, the common duct is elevated and the portal vein demonstrated to be free under the pancreas. To determine this, it may be necessary to ligate and divide the gastroduodenal artery at the upper border of the pancreas. If resection is then shown to be feasible, the prepyloric area of the stomach is divided between clamps. Careful

The resection is completed by dissection of the uncinate process, and the entire block is removed in one piece.

The reconstruction is done in the following order. The pancreas is closed by mattress sutures, and a transfixion silk suture is passed through the duct of Wirsung proximal to the tie.<sup>9</sup> The pancreatojejunal anastomosis is then completed, utilizing the afferent loop of jejunum. In the one-stage procedure, anastomosis of the common duct is done 5 cm distal to the pancreatojejunal anastomosis over a tube, following which an end-to-end gastrojeju-

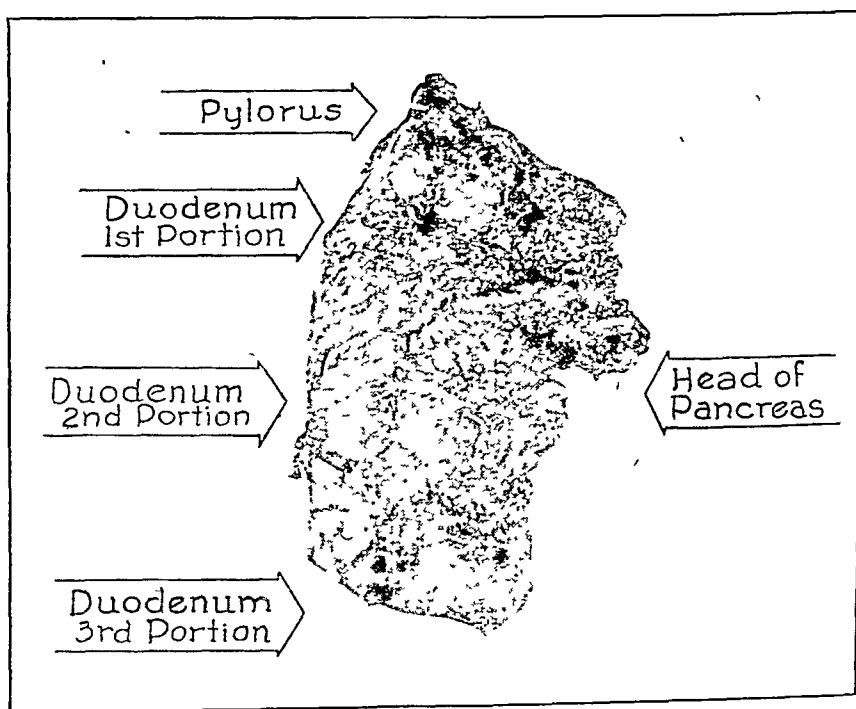


FIGURE 3. *The Serosal Surface of a Pancreatoduodenal Resection.*  
The pyloric end of the stomach, the duodenum and the head and neck of the pancreas are visible

dissection of the common duct must be done, and if a previous stage of cholecystjejunostomy has been performed, the common duct must be divided well below the entrance of the cystic duct. If there is any doubt of the patency of the cystic duct when the common duct is turned in, it must be reopened and implanted in the jejunum, leaving two biliary anastomoses. The pancreas is then elevated, with division at the neck if there is carcinoma of the ampulla and through the body if there is carcinoma of the head of the pancreas, followed by ligation of the duct of Wirsung. The junction of the third and fourth portions of the duodenum is severed in carcinoma of the ampulla, but in carcinoma of the head of the pancreas the jejunum is sectioned 5 cm. below the ligament of Treitz and the upper jejunum and fourth portion of the duodenum are withdrawn under the superior mesenteric vessels.

nostomy is carried out. If the latter is done to the efferent loop of jejunum, it is an end-to-side anastomosis and no enteroenterostomy is necessary, but if it is done proximally, it should be followed by the jejunojejunostomy.

#### CLINICAL MATERIAL

Eighteen patients have been submitted to pancreatoduodenal resection. Ten additional patients had a first-stage operation, with a second operation planned. One refused the second procedure, 1 was considered to be in too poor condition to withstand it, in 1 case operation was discontinued because of vessels resembling hemangioma throughout the operative field, 2 patients were found to be inoperable because of metastases, 1 had involvement of the superior mesenteric vessels, and 1 had a benign tumor that could be removed from the

## THE CARDINAL MANIFESTATIONS OF PAROXYSMAL TACHYCARDIA\*

## II. Vascular Collapse

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VASCULAR collapse is frequently associated with paroxysmal tachycardia. The medical literature consists for the most part of single case reports and reveals that whereas in some cases collapse is associated with rapid ventricular rates, in others it is absent with equally rapid rates.<sup>1-15</sup> <sup>116</sup> have observed vascular collapse in 15 of 125 cases of tachycardia, and have pointed out that it occurred only under specific conditions, thus justifying its designation as one of the cardinal manifestations of paroxysmal tachycardia. In the present study 128 new cases have been added to the 125 previously reported, making a total of 253. All cases had an electrocardiogram confirming the presence of an abnormal rhythm and providing the ventricular rate during the paroxysm. To evaluate the role of tachycardia in the genesis of vascular collapse, cases in which circulatory failure was ap-

or more in 18 cases, 180 to 199 in 9, 170 to 179 in 5 and less than 150 in 4 cases. There were no signs of organic heart disease in 12 patients, 2 of whom

TABLE 2. *Age Distribution of Cases with and without Collapse.*

AGE BY DECADES	ALL CASES WITH VASCULAR COLLAPSE	CASES WITH COLLAPSE AND VENTRICULAR RATES OF 180 OR MORE	CASES WITHOUT COLLAPSE AND VENTRICULAR RATES OF 180 OR MORE
First . . . . .	0	0	2
Second . . . . .	1	1	0
Third . . . . .	0	0	0
Fourth . . . . .	4	3	3
Fifth . . . . .	7	7	3
Sixth . . . . .	9	6	7
Seventh . . . . .	14	6	6
Eighth . . . . .	4	3	0
Ninth . . . . .	1	1	0
Totals . . . . .	40	27	21

TABLE 1. *Correlation Between Vascular Collapse and Ventricular Rate in Two Hundred and Fifty-Three Cases of Paroxysmal Tachycardia.*

VENTRICULAR RATE	CASES WITH COLLAPSE	CASES WITHOUT COLLAPSE	TOTAL CASES
Less than 180 . . . . .	13 (6%)	192	205
180 or more . . . . .	27 (56%)	21	48
Totals . . . . .	40	213	253

parent before the onset of paroxysmal tachycardia were excluded. This study accordingly concerns the 40 patients (16 per cent) in whom vascular collapse complicated paroxysmal tachycardia, and 21 in whom vascular collapse did not occur despite extremely rapid heart rates. This larger series has confirmed the previous conclusions and has furnished additional facts of clinical interest and importance.

## VASCULAR COLLAPSE

The ages in the 40 cases ranged from thirteen to eighty-eight years, with 4 cases in the fourth decade, 7 in the fifth, 9 in the sixth, 14 in the seventh and 4 in the eighth decade. Paroxysmal auricular tachycardia and paroxysmal auricular fibrillation were each present in 13 cases (33 per cent), and paroxysmal auricular flutter and paroxysmal ventricular tachycardia each in 7 cases (18 per cent). The ventricular rate ranged from 130 to 233, but was less than 180 in only 13 cases. The rate was 200

had hyperthyroidism; the ventricular rate in these cases was 200 or more in 6, 180 to 189 in 3, 170 to 179 in 2 and 140 in 1. It is noteworthy in itself that 12 of the 40 patients had normal hearts, but even more revealing is the fact that the ventricular rates were not significantly slower in the 28 patients with organic heart disease than in those with structurally normal hearts. Vascular collapse and paroxysmal tachycardia were noted in 9 cases with acute or recent myocardial infarction, the collapse and tachycardia occurring later than the tenth day in 7 of them; the ventricular rate was 200 or more in 3, 180 in 2, 170 to 179 in 2 and 160 and 145, respectively, in 2 cases. In 7 cases of coronary heart disease, with a past or present history of angina pectoris or old myocardial infarction or post-mortem evidence of coronary-artery disease, the rate was 200 or more in 3, 190 in 1, 187 in 2 and 160 in 1. There were 6 cases of mitral stenosis (1 with coro-

TABLE 3. *Distribution of Various Types of Tachycardia in Cases with and without Collapse.*

RHYTHM	CASES WITH VASCULAR COLLAPSE		CASES WITHOUT VASCULAR COLLAPSE*	
	NO.	PER-CENTAGE	NO.	PER-CENTAGE
Paroxysmal auricular fibrillation	13	33	7	33
Paroxysmal auricular flutter	7	18	1	5
Paroxysmal auricular tachycardia	13	33	10	48
Paroxysmal ventricular tachycardia	7	18	3	14

\*Ventricular rate 180 or more.

nary heart disease), and the ventricular rates were 200 or more in 4, 187 in 1 and 140 in 1. A case of subacute bacterial endocarditis and dissecting mycotic aneurysm of the aortic valve had the slowest ventricular rate in the entire series, namely, 130. There were 2 cases of aortic and mitral valvular disease with ventricular rates of 170 and 200, re-

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Because of the painless jaundice in all but 1 of 15 cases, it is evident that the diagnosis of carcinoma of the pancreas, ampulla or biliary tract should have been made oftener.

### Pathology

Thirteen of the 18 patients had carcinoma of the ampulla, although one of these was a carcinoid without metastasis; 3 had cancer of the pancreas; 1 had a large carcinoma of the second portion of the duodenum, and in 1 patient no cancer was found. This high preponderance of carcinoma of the ampulla in this series of 18 cases may give an incorrect idea of the incidence of malignancy in this area, since in many of the patients with carcinoma of the pancreas the process was too advanced for resection. In 1 case, resection was carried out, but without question some cancerous tissue was left. The fact that so few cases of carcinoma of the pancreas are suitable for resection makes us believe that the operation of pancreatoduodenal resection at present offers little hope for any case of extensive carcinoma of the head of the pancreas.

### Operation

Five patients had a one-stage pancreatoduodenal resection, with 1 death. The two-stage operation, as described by me,<sup>9</sup> was employed in 13, with 2 deaths. One patient had had a first-stage cholecystoduodenostomy performed elsewhere, and a second had had a two-stage operation elsewhere that was discontinued because of hemorrhage. These cases were of course listed under two-stage resections, although only one operation in each case was done by us.

The 3 deaths give an operative mortality of 17 per cent. The first patient operated on in 1939, died of hemorrhage. This occurred through an external pancreatic fistula and did not seem to be alarming in amount, but the patient succumbed two days later, on the seventeenth postoperative day. An autopsy did not reveal the site of bleeding, and no other cause for death could be determined; the death was listed as having been due to secondary hemorrhage. Because of reaction around the ligated stump of the gastroduodenal artery it was suspected that the hemorrhage had occurred from this source. The second death, in March, 1943, occurred from shock and anuria twenty-eight hours after operation. The third death, in May, 1943, occurred sixty-two days postoperatively. Autopsy showed pyelonephritis, with cortical abscesses, retroperitoneal sepsis and pericarditis.

### Subsequent Results

These patients have been observed over too short a period of time to report late results. One patient has been well for two years, 5 for eighteen months, 4 for a year, and 3 are in good condition, having been operated on within the past year.

There have been 2 deaths subsequent to discharge from the hospital. The first of these patients had an extensive carcinoma of the duodenum with lymph-node metastases and died eight months postoperatively. The second had an extensive carcinoma of the pancreatic head, and at the time of operation it was thought that some cancerous tissue was left. Death followed in ten months from recurrence with generalized abdominal metastases.

Thirteen of the 18 patients are living and in good condition. One patient has had mild recurrent epigastric discomfort, and 2 have had transient attacks of chills and fever. None have had recurrent jaundice. All have maintained their nutrition.

### SUMMARY

Eighteen pancreatoduodenal resections are reported, with 3 deaths, an operative mortality of 17 per cent. Clinical data are presented briefly.

The general plan of operative management is discussed. The one-stage operation was employed in 5 cases, and the two-stage operation in 13. Since many patients are over sixty years of age, have severe obstructive jaundice and are in poor condition, the two-stage operation is considered necessary in most cases. An antecolic long-loop cholecystojejunostomy is recommended, since it permits rehabilitation and does not complicate the resection. Restoration of the external pancreatic juice to the intestine is accomplished by direct anastomosis of the duct of Wirsung to the jejunum as a means of avoiding the serious complication accompanying pancreatic fistula, and in order that normal pancreatic and digestive function may be accomplished. Antecolic gastric, biliary and pancreatic anastomoses are advised.

Results for a period up to two years are reported, with satisfactory results in 13 of 18 patients.

Present experiences demonstrate that pancreatoduodenal resection for carcinoma can be successfully carried out.

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189 in 8 and 190 to 199 in 2. The rate in 8 patients with normal hearts, including 2 cases of hyperthyroidism, was 200 or more in 6, 193 in 1 and 180 in 1. Paroxysmal tachycardia did not induce vascular collapse in 2 cases of acute myocardial infarction, 1 of which was further complicated by congestive failure; the ventricular rates were 188 and 187, respectively. The rates in 5 other cases of coronary heart disease — 1 of them with complicating hyperthyroidism — were 215, 190, 188, 187 and 180, respectively. In 3 cases of hypertensive heart disease the rate was 200, 200 and 180, respectively, and in a case of subacute bacterial endo-

at the faster ventricular rates, but promptly disappeared when the ventricular rates halved. Similarly, vascular collapse was not induced by paroxysmal auricular tachycardia at a rate of 150 in a patient with a normal heart, but promptly appeared a few days later with the onset of a second paroxysm at a rate of 186. The duration of the paroxysm and the type of cardiac mechanism do not appear in themselves to be decisive in provoking circulatory failure. The lesser incidence of paroxysmal auricular fibrillation and the correspondingly greater incidence of the other types of tachycardia in the cases with collapse than in the entire series are due to the fact

TABLE 5. *Data on Ten Cases of Congestive Heart Failure. Six with Vascular Collapse and Four without Vascular Collapse despite Ventricular Rates of 180 or More.*

CASE No.	AGE yr.	RHYTHM	VENTRICULAR RATE per min.	DIAGNOSIS	COMMENT
30	57	Paroxysmal auricular tachycardia	130	Subacute bacterial endocarditis; free aortic insufficiency.	Vascular collapse
46	41	Paroxysmal auricular fibrillation	210	Mitral stenosis	Vascular collapse
115	65	Paroxysmal auricular flutter	187	Mitral stenosis; coronary heart disease.	Vascular collapse; autopsy.
124	34	Paroxysmal auricular fibrillation	140	Mitral stenosis	Vascular collapse; pulmonary embolism and infarction; autopsy.
133	64	Paroxysmal auricular fibrillation	170	Mitral stenosis; aortic stenosis.	Vascular collapse
227	73	Paroxysmal ventricular tachycardia	200	Acute myocardial infarction	Vascular collapse
16	63	Paroxysmal auricular tachycardia	200	Pneumonia; diabetes.	No vascular collapse
18	54	Paroxysmal auricular tachycardia	215	Hypertensive and coronary heart disease	No vascular collapse; autopsy.
49	60	Paroxysmal auricular tachycardia	200	Hypertensive heart disease	No vascular collapse
127	44	Paroxysmal ventricular tachycardia	187	Recent myocardial infarction	No vascular collapse; autopsy.

carditis it was 200. Two patients with cardiac enlargement of undetermined etiology had ventricular rates of 187 and 214. Frank congestive failure was noted in 4 cases, and the rates were 215, 200, 200 and 187.

### DISCUSSION

When vascular collapse is associated with paroxysmal tachycardia, the one factor invariably present is an extremely rapid ventricular rate. The critical rate level for the induction of collapse is in the vicinity of 200, which is consistent with the observations of Wiggers<sup>17</sup> that the total cardiac output falls when the heart rate exceeds 180. That this is the only necessary factor is evident from the fact that collapse is induced by extreme rates in cases with normal hearts uncomplicated by severe infection, embolism, surgery and so forth. The importance of the rate is shown by 2 cases of paroxysmal auricular tachycardia with auricular rates of 233 and 214, respectively, and intermittent 2:1 auriculoventricular block; signs of circulatory failure were evident

that extremely rapid ventricular rates are less frequent in paroxysmal auricular fibrillation than with other mechanisms.<sup>16</sup> Congestive failure plays no part in the genesis of vascular collapse. The age factor is largely unimportant, except that circulatory failure may be induced by somewhat slower rates in the aged than in younger patients. With aortic valvular disease, collapse may be induced at rates considerably below the critical level.

Vascular collapse occurred in 27 of 48 cases with ventricular rates of 180 or more, but in only 13 of 205 cases in which the ventricular rate was less than 180; the view that an extremely rapid ventricular rate, and it alone, is responsible for circulatory failure is strengthened by a review of these 13 cases. One of the patients had mild collapse with a ventricular rate of 177, which is too near the critical rate level to require any comment; an eighty-year-old man had collapse with a rate of 170, and 2 patients had aortic valvular disease. Pulmonary embolism, in addition to paroxysmal tachycardia, was present in 7 cases and, as is well known, may itself be respon-

spectively. There was 1 case of cor pulmonale, with a ventricular rate of 187, 1 case of pericarditis with a rate of 214, 1 case of hypertensive heart disease with a rate of 150 and 1 case of heart enlargement of undetermined etiology with a rate of 166. Frank congestive failure was observed in only 6 cases, and the ventricular rates in these were 210, 200, 187, 170, 140 and 130, respectively. The slowest rates were noted in 7 cases complicated by pulmonary embolism — 140 in 2 cases and 150, 160, 166, 170

times. Paroxysmal auricular tachycardia with a ventricular rate of 170 induced vascular collapse in an eighty-year-old man; the heart was normal and there were no complicating factors; stimulation of the carotid sinus interrupted the tachycardia, with immediate resumption of a normal circulation. The last patient in this group had mild vascular collapse with paroxysmal auricular tachycardia and a ventricular rate of 177; his heart was normal, and although he was seventy years old, he had had similar

TABLE 4. *Cases of Vascular Collapse with Ventricular Rates of Less than 180.*

CASE No.	AGE yr.	RHYTHM	VENTRICULAR RATE per min.	DIAGNOSIS	COMMENT
9	53	Paroxysmal auricular fibrillation	160	Angina pectoris	Pulmonary embolism
12	64	Paroxysmal auricular fibrillation	170	Recent myocardial infarction	Pulmonary embolism
30	57	Paroxysmal auricular tachycardia	130	Subacute bacterial endocarditis; congestive failure.	Free aortic insufficiency
31	70	Paroxysmal auricular tachycardia	177	Normal heart	Mild collapse; attacks for 20 years.
124	34	Paroxysmal auricular fibrillation	140	Mitral stenosis; congestive failure.	Pulmonary embolism and infarction; autopsy.
133	64	Paroxysmal auricular fibrillation	170	Mitral stenosis; aortic stenosis; congestive failure	Aortic stenosis
145	64	Paroxysmal ventricular tachycardia	175	Recent myocardial infarction	Large pulmonary infarct
149	62	Paroxysmal ventricular tachycardia	145	Acute myocardial infarction	Recurrences of collapse later during normal rhythm
153	65	Paroxysmal auricular fibrillation	150	Hypertensive heart disease	Phlebitis; pulmonary embolism and infarction.
179	60	Paroxysmal auricular tachycardia	165	Large heart (questionable etiology)	Pulmonary embolism; shock continued after normal rhythm restored.
180	66	Paroxysmal auricular fibrillation	140	Normal heart	Phlebitis and pulmonary embolism
197	80	Paroxysmal auricular tachycardia	170	Normal heart	
235	62	Paroxysmal auricular fibrillation	160	Acute myocardial infarction	Shock appeared 4 hours after the onset of paroxysmal auricular fibrillation and chest pain; there was possible fresh myocardial infarct or possible pulmonary embolism with a probable toxic quinidine reaction

and 175, respectively, in 5. There were only 6 other cases in which the ventricular rate was less than 180. One of these patients had free aortic insufficiency, and another mitral and aortic stenosis. The third had chest pain and paroxysmal auricular fibrillation with a rate of 160 on the tenth day of acute myocardial infarction. Four hours after the onset of the arrhythmia and one and a half hours after the second intramuscular injection of quinidine, when the ventricular rate had dropped to 130, vascular collapse suddenly appeared and death occurred half an hour later. In another case, vascular collapse and paroxysmal ventricular tachycardia with a rate of 145 occurred on the thirteenth day after acute myocardial infarction. Quinidine restored normal rhythm, which was maintained until the patient's death fourteen days later; during this period the temperature and white-cell count were elevated and vascular collapse recurred several

attacks, according to his own statement, for twenty years.

#### EXTREMELY RAPID RATES WITHOUT VASCULAR COLLAPSE

Vascular collapse is not invariably induced when extremely rapid ventricular rates are attained. Forty-eight patients in this series had rates of 180 or more, but without vascular collapse in 21. The 2 youngest patients were two and six years old, respectively, and there were 3 patients each in the fourth and fifth decades, 7 in the sixth and 6 in the seventh decade. Seven patients (33 per cent) had paroxysmal auricular fibrillation, 10 (48 per cent) paroxysmal auricular tachycardia, 1 (5 per cent) paroxysmal auricular flutter and 3 (14 per cent) paroxysmal ventricular tachycardia. The ventricular rate was 200 or more in 11 cases, — the fastest rate being 250 in a two-year-old child, — 180 to

## MEDICAL PROGRESS

### SCARLET FEVER (Concluded)\*

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#### EPIDEMIOLOGY

There has been a marked decline in the severity of scarlet fever in the last thirty years.<sup>40</sup> The mortality rate has dropped materially in the northern states, but this has not been apparent in the South.<sup>41</sup> Furthermore, as pointed out by Stebbins,<sup>41</sup> where the incidence of scarlet fever has declined there is not always a comparable reduction in the incidence of other streptococcal infections. This statement applies more to states and municipalities than to military organizations.

In the last few years the newer technics of identifying beta-hemolytic streptococci have been used in several studies of the epidemiology of scarlet fever. These studies give a rational explanation of how this disease is spread from person to person and how epidemics start and spread, and point out the factors that appear to be necessary in the control of this disease. The work of Keefer and his associates<sup>38</sup> on the epidemiology of scarlet fever has already been described. Schwentker, Janney and Gordon<sup>4</sup> made a study of streptococcal infection in Rumania over a period of three years, and have pointed out many of the important factors having to do with the epidemiology of the diseases produced by this group of organisms. They found that there is a gross mathematical relation between the incidence of scarlet fever in a country and its latitude. In temperate countries, the logarithm of the morbidity was found to be directly proportional to the latitude, whereas in the tropics streptococcal diseases are rare. In this connection, they neglect to bring out that whereas these diseases are not prevalent at sea level in the tropics, they become extremely prevalent at high altitudes, as in Bogotá and Mexico City.

These authors noted that no one of several serologic types of streptococcus was universally responsible for the disease over the world, although in any given country one or a few types usually predominated. The incidence of any one type among the total scarlatinal strains varied from time to time, one type gradually diminishing as another increased in frequency. It was found that more than one group or type of streptococcus could be recovered from the throats of healthy carriers as well as those of convalescent carriers, but that

patients with acute disease usually harbored only one serologic type. In Rumania there was a cyclic rhythm in the gross and Group A carrier rates, the highest rate occurring during the late autumn and winter, and the lowest in the summer months. The same incidence with respect to season applies to New England, and this carrier rate is directly correlated with the incidence of streptococcal infections, which are also most frequent in the fall and winter and least prevalent during the summer months. In a study of the carrier problem in Rumania, Schwentker and his co-workers found that the gross and Group-A carrier rates bore a crude direct relation to each other, whereas the carrier rates for all groups other than Group A remained constant. They concluded that the incidence of scarlet fever is dependent on the carrier rate rather than the reverse.

In a study of the different serologic types present in the various villages in which the work was done, it was shown that all the known types of streptococci could be found but that the majority occurred only infrequently. In each village a few types predominated in general, but the outstanding bacterial flora was different for each community. Many of the types fluctuated in frequency of occurrence with time. The streptococcal types most frequently found in scarlet fever also caused most of the other streptococcal diseases in the same region. The same types that produced disease were also the ones that were prevalent in carriers. The differences in streptococcal flora between communities with and without scarlet fever were slight, and greater than between two different areas free from scarlet fever. From these facts it was concluded that some condition other than lack of scarlatinal strains must have been responsible for the absence of scarlet fever. A study was also made of the Dick reaction. It was found that in villages free of scarlet fever the distribution of positive Dick reactions in various age groups was the same as in other parts of the world, as has been described above. The percentage distribution of positive Dick reactions had much the same general pattern as the age distribution of cases of scarlet fever.

An epidemic of scarlet fever due to a Type 10 strain of hemolytic streptococcus was studied. Just before the outbreak of the epidemic there occurred an increase in the gross, Group A and Type 10 carrier rates, and this increase was maintained until almost the end of the epidemic. Patients who developed tonsillitis without a rash were shown to be infected with the same type of streptococcus.

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sible for vascular collapse. The data in the 2 remaining cases, presented above in detail in the section on vascular collapse, clearly indicate that factors other than tachycardia were present and at

TABLE 6. Analysis of the Forty-Eight Cases with Rates of 180 or More according to the Diagnosis and to Whether Vascular Collapse Occurred.

DIAGNOSIS	CASES WITH RATE OF 180-199	CASES WITH RATE OF 200 OR MORE	ALL CASES
Normal heart:			
Collapse .....	3	6	9
No collapse .....	2	6	8
Acute or recent myocardial infarction:			
Collapse .....	2	3	5
No collapse .....	2	0	2
Coronary heart disease:			
Collapse .....	3	3	6
No collapse .....	4	1	5
Mitral stenosis:			
Collapse .....	1	4	5
No collapse .....	0	0	0
Hypertensive heart disease:			
Collapse .....	0	0	0
No collapse .....	1	2	3
Other types of heart disease:			
Collapse .....	1	1	2
No collapse .....	1	2	3
Totals .....	20	28	48

least partly responsible for the circulatory failure; the late appearance of collapse, with sudden death shortly after its onset in one of them, and recurrence of collapse after restoration of normal rhythm in the other, are not to be expected when collapse is due solely to extreme tachycardia; an untoward quinidine reaction may have been present in one of the cases.

The question why extremely rapid rates induce collapse in some cases but not in others cannot be answered from the above data; even soon after recovery from vascular collapse unassociated with paroxysmal tachycardia, extremely rapid rates may fail to induce circulatory failure. It is interesting that, in the absence of complicating factors, the critical level for the ventricular rate is not lower in cases of myocardial infarction or other types of heart disease—with the exception of aortic valvular disease—than it is in normal hearts. Nevertheless, when the critical rate level is reached or surpassed, the susceptibility to collapse is somewhat different in the various groups. Vascular collapse is induced by rates of 180 or more in about half the cases with normal hearts and of those with coronary heart disease, in about three quarters of the cases of acute or recent myocardial infarction and in all the cases of mitral stenosis. Collapse did not occur in the 3 cases of uncomplicated hypertensive heart disease, a number too small to warrant any conclusions.

When vascular collapse is induced by paroxysmal tachycardia, it promptly disappears when the abnormal rhythm is abolished or a significant reduction of the heart rate is effected. When this does

not happen, some factor other than the tachycardia must have caused the collapse. Other factors must be sought also when collapse occurs with rates well under 200, except in cases of aortic valvular disease. The most frequent additional factor in this series was pulmonary embolism.

SUMMARY

The clinical data of 253 cases of paroxysmal tachycardia are analyzed with reference to the occurrence of vascular collapse.

Vascular collapse occurs under constant conditions and is therefore one of the cardinal manifestations of paroxysmal tachycardia; it occurs in 16 per cent of the cases.

Extreme tachycardia itself induces vascular collapse in more than half the cases with rates at or above the critical level, which is in the vicinity of 200; below this level, collapse is not induced by tachycardia alone. The critical level is not lower in cases of myocardial infarction or other types of heart disease, with the exception of aortic valvular disease, than in normal hearts.

Extremely rapid ventricular rates induce vascular collapse in about half the cases with normal hearts and with coronary heart disease, in about three quarters of the cases of acute or recent myocardial infarction and in all the cases of mitral stenosis.

Causes other than tachycardia must be suspected when collapse is associated with rates well under 200 or when termination of the abnormal rhythm or significant reduction of heart rate is not promptly followed by resumption of a normal circulation.

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## MEDICAL PROGRESS

### SCARLET FEVER (Concluded)\*

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#### EPIDEMIOLOGY

There has been a marked decline in the severity of scarlet fever in the last thirty years.<sup>40</sup> The mortality rate has dropped materially in the northern states, but this has not been apparent in the South.<sup>41</sup> Furthermore, as pointed out by Stebbins,<sup>41</sup> where the incidence of scarlet fever has declined there is not always a comparable reduction in the incidence of other streptococcal infections. This statement applies more to states and municipalities than to military organizations.

In the last few years the newer technics of identifying beta-hemolytic streptococci have been used in several studies of the epidemiology of scarlet fever. These studies give a rational explanation of how this disease is spread from person to person and how epidemics start and spread, and point out the factors that appear to be necessary in the control of this disease. The work of Keefer and his associates<sup>38</sup> on the epidemiology of scarlet fever has already been described. Schwentker, Janney and Gordon<sup>4</sup> made a study of streptococcal infection in Rumania over a period of three years, and have pointed out many of the important factors having to do with the epidemiology of the diseases produced by this group of organisms. They found that there is a gross mathematical relation between the incidence of scarlet fever in a country and its latitude. In temperate countries, the logarithm of the morbidity was found to be directly proportional to the latitude, whereas in the tropics streptococcal diseases are rare. In this connection, they neglect to bring out that whereas these diseases are not prevalent at sea level in the tropics, they become extremely prevalent at high altitudes, as in Bogotá and Mexico City.

These authors noted that no one of several serologic types of streptococcus was universally responsible for the disease over the world, although in any given country one or a few types usually predominated. The incidence of any one type among the total scarlatinal strains varied from time to time, one type gradually diminishing as another increased in frequency. It was found that more than one group or type of streptococcus could be recovered from the throats of healthy carriers as well as those of convalescent carriers, but that

patients with acute disease usually harbored only one serologic type. In Rumania there was a cyclic rhythm in the gross and Group A carrier rates, the highest rate occurring during the late autumn and winter, and the lowest in the summer months. The same incidence with respect to season applies to New England, and this carrier rate is directly correlated with the incidence of streptococcal infections, which are also most frequent in the fall and winter and least prevalent during the summer months. In a study of the carrier problem in Rumania, Schwentker and his co-workers found that the gross and Group-A carrier rates bore a crude direct relation to each other, whereas the carrier rates for all groups other than Group A remained constant. They concluded that the incidence of scarlet fever is dependent on the carrier rate rather than the reverse.

In a study of the different serologic types present in the various villages in which the work was done, it was shown that all the known types of streptococci could be found but that the majority occurred only infrequently. In each village a few types predominated in general, but the outstanding bacterial flora was different for each community. Many of the types fluctuated in frequency of occurrence with time. The streptococcal types most frequently found in scarlet fever also caused most of the other streptococcal diseases in the same region. The same types that produced disease were also the ones that were prevalent in carriers. The differences in streptococcal flora between communities with and without scarlet fever were slight, and greater than between two different areas free from scarlet fever. From these facts it was concluded that some condition other than lack of scarlatinal strains must have been responsible for the absence of scarlet fever. A study was also made of the Dick reaction. It was found that in villages free of scarlet fever the distribution of positive Dick reactions in various age groups was the same as in other parts of the world, as has been described above. The percentage distribution of positive Dick reactions had much the same general pattern as the age distribution of cases of scarlet fever.

An epidemic of scarlet fever due to a Type 10 strain of hemolytic streptococcus was studied. Just before the outbreak of the epidemic there occurred an increase in the gross, Group A and Type 10 carrier rates, and this increase was maintained until almost the end of the epidemic. Patients who developed tonsillitis without a rash were shown to be infected with the same type of streptococcus.

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All those who came down with scarlet fever were shown to be Dick positive. Among those who escaped infection some were Dick positive and others Dick negative; these did not become ill in spite of the fact that they were proved by culture to be harboring the causative agent. It was concluded that they must have had a sufficient degree of antibacterial immunity to protect them.

These authors give a concise and clear description of their conception of the epidemiology of scarlet fever:

A scarlatinal strain of streptococcus, either newly introduced or already present in a community, is distributed throughout the population. The number of persons reached depends on the distribution factor, as previously described [measured by the carrier rate]. The distribution factor determines the degree of dissemination of the streptococcus in the community, and by the law of chance, the greater the dissemination, the greater the number of persons who will come in contact with the organism. Some persons escape contact with the streptococcus entirely; these naturally remain well. Among the others who are reached by the organism, some will be resistant by virtue of antibacterial immunity. Regardless of their Dick reaction or antitoxic immunity, they remain well. These persons either eliminate the organism promptly or become healthy carriers. Those without antibacterial immunity sicken. The Dick-positive individuals, having no antitoxic immunity, develop scarlet fever; those with antitoxic immunity have streptococcal tonsillitis without the scarlatinal rash. The difference is purely clinical. Should the portal of entry be other than the nasopharynx, the relationship is still the same. Puerperal fever may develop with or without the scarlatinal rash; or erysipelas or some other kind of infection may occur. From the three groups of individuals who harbor the streptococcus, the organisms are still further distributed and the cycle repeats itself.

Schwentker, Hodes, Kingsland, Chenoweth and Peck<sup>42</sup> studied a company of sailors in "boot training" in whom there occurred an outbreak of streptococcal infection. Six different types of streptococci were found to be responsible for sickness in the company. Of these, Types 1 and 6 were outstanding. Together they accounted for 30 of 42 cases of infection. These types did not cause scarlet fever. The 2 cases of scarlet fever that occurred were both due to Type 3. The percentage distribution of the various types was the same among cases of illness as in normal carriers. The distribution of the various types among normal carriers in six other companies on the station was practically the same as in the study company. In all companies, Types 1 and 6 predominated. Nevertheless, among cases of scarlet fever occurring at the station, Types 3 and 19 were outstanding. No case of scarlet fever due to Type 6 was discovered, and only 2 were due to Type 1. It appeared that the streptococci present at the station could be divided into two types — those that were highly pathogenic but had little scarlatigenic ability, and those that were scarlatigenic as well as pathogenic.

The carrier rate of streptococci was found to be high in the groups that were studied. Whereas the rate in the general population is usually 10 per cent, at this station it was found to be as high as 69 per cent. Where more than one type of streptococcus was active during an outbreak, the number of cases due to each type was found to be proportional to the carrier rate for the respective type. This makes it appear that the carrier was instrumental in transmitting the disease. The high carrier rates were found to develop among the men during the period of training, because only 4 per cent of incoming inductees were found to harbor beta-hemolytic streptococci.

A group of 73 men who did not develop any illness were also studied. These men remained well in spite of the fact that as many as five different types of streptococci of known pathogenicity were recovered from their throats. The Dick reaction apparently played no role in resistance to infection, since the amount of illness in Dick-negative men was proportionately the same as that in Dick-positive ones. Some persons were found to resist infection with one type of streptococcus but became ill when infected with another type. No person was found who had two illnesses due to the same serologic type of streptococcus. It is interesting that the authors were able to show that some of the strains isolated from those who had a streptococcal infection without a rash — that is, no scarlet fever — were capable of producing erythrogenic toxin.

Schwentker<sup>43</sup> also studied the role of the carrier in the spread of an epidemic of streptococcal infection. He observed an epidemic of scarlet fever in an Army camp due to an organism that gave reactions with both Types 17 and 23 by the Griffith technic and with Type 19 by the Lancefield precipitin method. These findings were due to the fact that the organism contained T antigens of both Types 17 and 23 but M antigen only of Type 19. The number of cases of scarlet fever in different companies studied varied from zero to 10 per cent. The case incidence was found to be related to the carrier rate for the Type 19 strain of streptococcus causing the outbreak. The logarithm of the incidence of scarlet fever was directly proportional to the Type 19 streptococcus carrier rate. The same relation was found to exist between the incidence rate of the disease and the gross (all groups) and Group A carrier rate, but in each of these cases it was merely a reflection of the Type 19 relation. The carrier rates for groups other than Group A and for all Group A strains except for Type 19 were found to be roughly the same in all companies.

In 1944, Coburn<sup>44</sup> reported some studies on the problem of the role of the carrier in the transmission of streptococcal disease. He described two outbreaks set up by carriers. In a group of 200 patients with throat infections due to Type 19 streptococcus,

some of whom had scarlet fever whereas others did not, there were two persons who proved to be dangerous carriers after discharge from the hospital, both giving rise to additional cases. One of these men had an acute pharyngitis followed by mastoiditis, sinusitis and bronchitis. He gave rise to 4 cases of scarlet fever or acute pharyngitis during readmission to the hospital for a mastoidectomy. The other man had a sinusitis and a focal pneumonitis following an attack of scarlet fever and later, while in an orthopedic ward containing 40 bed patients for observation following a minor head injury, was responsible for 16 cases of streptococcal infection in that ward. In neither carrier was the number of streptococci in the throat culture found to be large, and in neither of them was the organism highly invasive. In both, however, the communicability was high and outbreaks occurred. Coburn believes that a high degree of communicability, and thus a dangerous carrier state, may be acquired by the streptococcus during secondary infections and during an outbreak of virus infections of the respiratory tract. The latter finding is in direct contrast to that of Schwentker, Janney and Gordon, who were unable to demonstrate any effect of the incidence of the common cold or the nonspecific infection referred to as "influenza" on the incidence of streptococcal infection.

Communicability in the two patients described by Coburn was thought to cease when the infectious process subsided under the influence of sulfonamides. In discussing the property of communicability, Coburn expresses the belief that this is acquired by an adaptive change in the bacteria with relation to the changing immune state in the host under conditions of an infection in which neither the host nor the bacterium can promptly establish supremacy. Because of the change, the bacteria become able to multiply in the presence of inhibitory substances present in the normal mucous membranes and thus become host-fast. This property may be quickly lost, but so long as it exists the organisms have a high degree of communicability. Coburn speculates that fundamentally this phenomenon may depend on the development of adaptive enzyme systems.

A study of the factors concerned in the transmission of streptococcal infections has been made by Hamburger.<sup>45</sup> It was found that when only as few as one or two carriers were present, cross-infection spread rapidly on open wards where there were patients with streptococcal infections. On the other hand, cross-infection might not occur if as high as 50 per cent of the patients on a ward were harboring Group A streptococci in their throats. Subclinical cross-infections by hemolytic streptococci were found to be not infrequent. Patients who were recovering from German measles seemed to share the well-recognized susceptibility of patients with measles to

streptococcal infection. These authors also point out that there is insufficient proof that because a person is a streptococcal carrier he is responsible for cases of infection, since he may be harboring a serologic type entirely distinct from that producing disease.

Hamburger<sup>46</sup> also made a study of the content of the saliva of 156 patients who had beta-hemolytic streptococci in their throats, studying this as a factor in the transmission of streptococcal infections. He found that in the acute stages of scarlet fever over 80 per cent of the patients had the same serologic type of beta-hemolytic streptococci in the saliva as in the throat. In the remainder of the patients no streptococci were demonstrated in the saliva. Several day-to-day patterns of streptococcal content of the saliva were found to exist. In 51 per cent of the patients, the number of hemolytic streptococci in the saliva diminished with the passage of time, usually gradually but in some cases abruptly. In 25 per cent, there was no change in the salivary flora during a period of weeks; about half these showed the presence of streptococci in the saliva, and the other half showed none. Hamburger could find no significant difference in the number of hemolytic streptococci in the saliva at various stages of the scarlet fever as compared with that from cases of tonsillitis and pharyngitis without a rash. In patients who had had their tonsils removed it was found that hemolytic streptococci were present in smaller numbers and for shorter periods than in those in whom the tonsils were still present.

Hamburger and his associates<sup>44</sup> also made a study of the air and the floor dust in a ward and the bedclothes in their relation to the transmission of streptococcal infections. They found that air-borne organisms were present in large numbers in wards in which streptococcal disease was present, and that these were most numerous around the beds of patients whose respiratory secretions contained the largest numbers of streptococci. They showed that the number of organisms in the air is important in any consideration of the role that air plays in transmission of disease, and that even a small number of streptococci in the air are capable of producing disease in a susceptible person. Thus, a technician who was working on a streptococcal ward became infected when the number of organisms present in the air was shown to be less than 1300. It is pointed out that the reservoir from which the organisms get into the air is the floor dust and the bedclothes of patients with streptococcal infections. Therefore, the control of air-borne streptococcal infection in hospital wards may be largely a question of control of the secondary reservoirs in dust and bed linen. Hodes and his co-workers<sup>47</sup> have studied scarlet fever as an air-borne infection. They conclude that the direct transmission by air from a patient with scarlet fever is a more important means of spread

than is the general reservoir of air. Wheeler and Jones<sup>48</sup> have demonstrated that one of the most significant factors in the genesis of epidemics is the rapid introduction of susceptible persons into an infected population, as in the reception of recruits.

From these more recent studies on the epidemiology of scarlet fever several pertinent facts become obvious. First, epidemics of this disease are usually due to one or two serologic types of streptococcus, whereas sporadic cases may be due to any of the types that have been described. Furthermore, just preceding and during an epidemic there is often an increase in the carrier rate of the serologic types that are most prevalent in the sick. The exact role of the healthy carrier in the transmission of streptococcal infections is not clear. The studies of Foley, Wheeler and Aycock<sup>49</sup> indicate that the spread of scarlet fever through secondary cases is not limited to case-to-case transfer, but includes nonscarlet-fever and subclinical infection as well as intermediate carriers. Schwentker, Janney and Gordon<sup>4</sup> and some of the other workers who have been cited maintain that the so-called "healthy carrier" may be an important factor in the dissemination of streptococci, with the subsequent production of actual infection. Coburn's<sup>44</sup> hypothesis regarding the adaptive abilities of the streptococci with respect to their degree of communicability deserves further investigation. Hamburger's<sup>14</sup> investigations have emphasized the well-known significance of the role played by air, floor dust and bedclothes in the transmission of streptococcal infections in hospital wards. The crowding together of large numbers of men from various parts of the country in the various establishments of the armed forces has afforded an exceptional opportunity for studying the epidemiology of outbreaks of streptococcal disease in sufficiently large numbers to yield invaluable data, in drawing conclusions from which the greatest care must be taken. There is still much to be learned concerning the epidemiology of the streptococcal infections.

#### METHODS OF CONTROL

Granting that scarlet fever is merely one manifestation of streptococcal infection and is dependent on the ability of the invading strain to elaborate an erythrogenic toxin in a susceptible host, it becomes clear that many persons may harbor toxin-producing strains without manifesting signs of scarlet fever. First, the person may be a carrier and thus show no manifestation of disease. It has been seen that the carrier rate of the epidemic strain often rises abruptly prior to and during an epidemic, but this fact does not establish that cases of scarlet fever originate from carriers. The recent studies of Hamburger<sup>45</sup> in an Army hospital cast some doubt on the part played by the healthy carrier in the spread of scarlet fever. Thus, although the carrier index may

give valuable warning concerning a probable outbreak of an epidemic of scarlet fever and the etiologic type, the carrier is not necessarily the means of spreading the disease, unless he himself succumbs to an invasion of the streptococcus and becomes ill. Further studies are necessary to determine whether as a result of the illness he may change from a harmless carrier to a dangerous one. The complexity of this problem from the standpoint of extremely mild or so-called "missed" cases is apparent.

The carrier here referred to is not to be confused with the patient who is convalescent from scarlet fever and still harbors the etiologic strain in some localized infection, whether this be a subacute rhinitis, tonsillitis, otitis media, paronychia or discharging wound. Aside from such a low-grade infection he may be afebrile and enjoy good health, but such a person is not a healthy carrier in the true sense of the term.

After uncomplicated scarlet fever the upper respiratory tract usually returns to normal by the end of the second week in adults and by the end of the third week in children. It is often difficult to say just what constitutes normality, since only parts of the upper respiratory tract are visible on examination. Therefore, some patients may seem to be clear of infection at the end of the isolation period and yet be capable of infecting others. If this were the only source of scarlet fever, one might consider the advisability of a longer period of isolation, but prolonged isolation has not reduced the incidence of scarlet fever. A small percentage of the uncomplicated cases are still infectious after four weeks. When scarlet fever is epidemic, there are always many persons about with sore throats but without the rash who disseminate the same streptococci as freely as those with the full-blown rash—indeed, much more so, since they are apt to be out and about rather than confined to bed. This is the explanation of the inability to control scarlet fever adequately by isolation in the home or in the hospital. If all patients with streptococcal disease were isolated instead of only those with one manifestation of streptococcal disease, something approaching control might be accomplished. But here again one is confronted by the fact that streptococcal infections, as determined by the presence of antistreptolysin, may be so exceedingly mild as to go unnoticed.<sup>4,60</sup> The role played by such subclinical cases in the spread of these infections is unknown. Certainly any attempt to control scarlet fever by quarantining carriers is impractical. Likewise it is difficult to control the influx of susceptible persons into an infected population. This has, however, been done with success in controlling an epidemic.<sup>47</sup> Thus, stopping the reception of raw recruits stops the spread of the disease as definitely as when new patients are refused admission to a ward where scarlet fever has broken out. Without new fuel a fire dies out.

In certain streptococcal epidemics an extremely high proportion of the cases exhibit scarlet fever. In others the opposite is true. In either instance it is inconsistent to isolate those with a rash for four weeks and to isolate the others for only the duration of the fever or not at all.

The new conception of scarlet fever has brought about a reduction of the isolation period in many cities in the United States. Three weeks for children and two weeks for those over seventeen years of age are now recommended by the Massachusetts State Department of Health. This is a gesture in the right direction, but it is still arbitrary. In Bergen and Trondheim in Norway, prior to the German invasion, scarlet fever was left to the attending physician to handle as a streptococcal infection, the rash being disregarded.<sup>18</sup> After eighteen years the results were sufficiently satisfactory to justify continuing the abolition of any set period of isolation. Aberdeen in Scotland followed this example and was still satisfied with the ruling after five years of a similar experiment.

#### *Hospitalization*

Hospitalization for streptococcal disease, including scarlet fever, should depend on circumstances. Isolation at home is desirable if the case is mild or moderate and exhibits no serious complications. The patient with a mild case who is placed on an open scarlet-fever ward is more liable to have a relapse and to have complications than if he were left at home. Poverty or unco-operative parents may be proper indications for hospitalization. Hospitalization is desirable in all severe cases and in all threatening complications, such as mastoiditis, sinus empyema and nephritis. Stockholm furnishes an excellent example. There, according to the latest accounts,<sup>51</sup> hospitalization for scarlet fever is required by law. Every case goes to the hospital, not because hospitalization has reduced the incidence of scarlet fever, but because the mortality rate has been found to be lower in the hospital in spite of open ward care than in the home. In other words, hospitalization affords better results through the prompt and effective handling of complications. If all patients with severe cases and complications were promptly hospitalized, the same good results would be obtained. Every possible effort should be made to avoid the overcrowding of scarlet-fever wards. The policy in this regard at the Belmont Hospital in Worcester deserves the greatest praise.

The hospital, then, should serve for those cases arising in homes where facilities for good care do not exist. It stands to reason that hospitalization is necessary for those mild cases that arise in military establishments and in boarding schools, colleges and other institutions where people are herded together in dormitories. Thus it is that in a large educational center, such as Greater Boston, adequate facilities for the hospitalization of upper

respiratory streptococcal disease should be available; furthermore, such hospitalization to be effective as a means of control should not be confined to those manifesting the rash of scarlet fever. It is particularly desirable that patients should be sent to a hospital when other members of the household are food handlers. Thus, hospitalization does play its part in the control of the disease. It should by no means be a routine procedure but should be applicable only to the exigencies of the individual situation.

#### *Inconsistencies in Regulations*

Not long ago a nurse after attending a case of scarlet fever was required to take a week off before signing on again for general nursing, in spite of the fact that she took a bath and changed her clothes on coming off the contagious case, whereas the doctors who insisted on this outrageous ruling had so little conception of contagious technic that they often went directly to other patients without even washing their hands. Other doctors donned caps, gowns and masks, insisted on having sheets soaked in bichloride of mercury hung in the doorway, and after examining the patient put their hands in their pockets to get their watch, glasses, handkerchief or thermometer. They then relied on dipping their hands in an antiseptic solution rather than washing them in soap and water. It is well to remind the medical profession of these sins of the past. Or shall it be admitted that the contagious technic of too many eminent physicians is vastly inferior to the aseptic technic of all eminent surgeons?

A child is sent to the hospital with scarlet fever, and at the same time another child in the family has a sore throat. The second child is not allowed at school but plays with her schoolmates on the street and goes to motion-picture shows. Any attempt to curtail the second child's activities is objected to by the parents on the ground that the child with the scarlet-fever case has been isolated in the hospital and that the other child has only a sore throat. Education of the public is sorely needed, but what chances are there of impressing the public when there is no agreement on isolation periods? The State Department of Public Health merely makes recommendations regarding isolation, whereas the local boards of health make the rules. Hence it is that in Greater Boston there is a wide variation in the requirements. A patient over seventeen years of age with uncomplicated scarlet fever is isolated for two weeks in Boston and Newton, for three weeks in Cambridge and Brookline and for four weeks in Lexington. If he lives in Boston he can go back to work in Lexington for the last two weeks of his convalescence, because Lexington has no report of his having had scarlet fever. The ignoring of the advice of the Department of Public Health by some local authorities leads to confusion and to lack of confidence in the methods of control.

In a certain military establishment the practice is to hospitalize all patients with upper respiratory streptococcal disease under the diagnosis of streptococcosis, and to isolate those with uncomplicated cases of scarlet fever. At the end of not over fourteen days these patients are allowed to leave by the main gate and to mingle with the townspeople. But these same military authorities insist that a carpenter employed in the erection of a new building in this establishment shall be laid off work for four weeks without pay because his young son has scarlet fever at home. It is, indeed, extremely difficult to educate the public to co-operate with the medical profession in the control of streptococcal disease when the laity sees the perpetration of such glaring inconsistencies.

### *Chemoprophylaxis*

The control of streptococcal infections and their sequelae, including rheumatic fever, through mass prophylaxis with small doses of sulfonamides has been carried out extensively in the last two years.<sup>47, 52-57</sup> The morbidity rate has been a serious problem in certain localities where these organisms flourish. Several recent reports in the literature indicate a successful program of control. Sulfonamide-resistant strains, however, are beginning to show up to a disturbing extent in certain localities.

Watson and his co-workers<sup>55</sup> reported their results in a study of the use of sulfadiazine in a Navy establishment in 1943. They were faced by an epidemic of scarlet fever due to a Group A, Type 19, beta-hemolytic streptococcus. As soon as the epidemic began all the personnel at the station were given 0.5 gm. of sulfadiazine twice a day. During the first week after the start of the sulfonamide therapy, the incidence of scarlet fever dropped markedly. In another group of men who did not receive daily dosage of the sulfonamide the incidence of scarlet fever remained high. When this second group was given the same dosage of sulfadiazine, there was a similar reduction in new cases. After the sulfonamide was discontinued scarlet fever remained absent. The carrier rate for Type 19 still remained high, although there was some reduction. The average blood level for the drug in the men who were treated was 2.5 mg. per 100 cc. Of the several thousand men treated prophylactically only 3 developed toxic manifestations in the form of a rash. No severe toxic reactions were observed.

A study of the same problem in the Army Air Forces by Holbrook<sup>53</sup> showed that when acute rheumatic fever became prevalent it was always preceded by a high incidence of hemolytic streptococcus infections. A 50 to 75 per cent reduction in the incidence of respiratory diseases and streptococcal infections was accomplished by the use of sulfadiazine prophylaxis under carefully controlled conditions in a significantly large troop population. A study of the data indicated that a reduction in

the incidence of rheumatic fever paralleled the reduction in the occurrence of respiratory and streptococcal diseases.

Coburn<sup>56</sup> has reported his observations on the use of sulfadiazine prophylaxis against streptococcal infection in a group of 30,000 men stationed at three different Navy camps. It was found that the ingestion of 1 gm. of the drug daily accomplished the following things: outbreaks of streptococcal infection were checked at their onset, well-advanced outbreaks of streptococcal disease appeared to be checked in their spread, and 85 per cent of the susceptible recruits were protected from implantation with bacterial respiratory pathogens. It seemed that a continuous daily dosage of 0.5 gm. of sulfadiazine yielding an average blood concentration of 1.4 mg. per 100 cc. and one of 0.8 mg. per 100 cc. in the respiratory secretions was almost 85 per cent effective in preventing implantation of *Str. haemolyticus*. The only untoward effects noted in this experiment in mass sulfadiazine prophylaxis were the occurrence of evanescent rashes in 0.5 per cent of the patients treated and severe constitutional reactions in 0.01 per cent.

The largest group of subjects in whom the experiment of mass prophylaxis with sulfadiazine has been attempted is mentioned in a recent report by the Bureau of Medicine and Surgery of the Navy Department,<sup>58</sup> covering observations carried out for a period of six months, with 600,000 men receiving daily doses of the drug. It was found that sulfadiazine, in either prophylactic or therapeutic doses had little effect on the throat flora of carriers of hemolytic streptococci. Implantation of streptococci was prevented regardless of the pathogenicity of the strains that were prevalent, although in some instances the organisms were able to overcome the inhibitory effects of sulfadiazine. This occurred after the drug in doses of 1 gm. daily had been ingested for several weeks, and was observed in areas where exposure to streptococcal infection was greatest and at times when the incidence of measles was high. Usually, however, it was evident that the presence of sulfadiazine in the secretions of the nasopharynx prevented the implantation of a new strain of hemolytic streptococcus and prevented frank infection in 95 per cent of the persons given the drug.

The percentages of untoward reactions observed were the same as those previously noted by Coburn<sup>56</sup> in the study of chemoprophylaxis in a smaller group of naval personnel. It is pointed out that coincident virus infections, particularly measles and influenza, increased the communicability of hemolytic streptococci, but that prophylaxis with sulfadiazine was highly effective in preventing the implantation of the bacteria in the upper respiratory tract of susceptible groups of persons living in camps in which measles was present. No sulfonamide-resistant strains were encountered, and there was no evidence

of such resistance during the six months that the study was carried out. There is some suggestion, however, that in the final month Type 19 may have developed some degree of fastness to the sulfadiazine, since at that time this organism became the prevalent one at several establishments. The importance of this problem to the Navy is stressed by the following quotation:

In these groups of naval personnel a saving of a day per man per month can be expected when bacterial respiratory pathogens are active. If the center's recruit complement is 50,000 and all hands receive sulfadiazine prophylaxis, one can anticipate a saving of 30,000 hospital days each month during seasons conducive to respiratory diseases. This is equivalent to freeing a 1000-bed hospital and all the labor and personnel associated with the care of the sick.

Keith and his associates<sup>57</sup> found that sulfadiazine in 1 gm. daily doses reduced hospital admissions for nasopharyngitis and scarlet fever to one third in a station of the Canadian Navy. Hodges<sup>54</sup> found this drug equally effective in this respect among troops in the United States Army.

The data that have been presented on the effect of prophylaxis with small doses of sulfadiazine for the prevention of outbreaks of scarlet fever and for the control of epidemics already under way are indeed impressive. The effect that this program has had in the saving of man-hours of duty in the armed forces has certainly been extremely helpful to the war effort.

Although mass prophylaxis with sulfonamides has been used extensively and with striking success in the armed forces, it must be kept in mind that this was carried out under medical supervision. This, of course, could be done under equally good medical supervision in boarding schools and similar institutions, but it is questionable whether it should be recommended for the population at large. Furthermore, tabulated reports from the stations where sulfonamide-resistant strains prevail have not been published, and we have yet to be told whether such mass prophylaxis encourages the development of sulfonamide-resistant strains.

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The recognition that scarlet fever is not a disease entity is a milestone of progress, but there is still much to be learned about the pathogenesis of scarlet

fever and its complications, its mode of spread and the possible role of carriers. Active immunization is a valuable means of protection, but this is indicated only where the chances of exposure are great, as in nurses' training schools. Great care should be taken in the selection of those to be immunized, as well as in the method employed. Serum therapy and chemotherapy have proved to be effective weapons in prophylaxis and treatment, but both these measures have distinct indications and definite limitations.

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31191

### PRESENTATION OF CASE

A sixty-nine-year-old gateman was admitted to the hospital because of jaundice, nausea and vomiting.

Three weeks before admission he noticed that his abdomen had become quite distended, and six days before entry he developed nausea and vomiting, which persisted until admission. He also observed that the urine was "dark." During the week before admission he passed only an occasional small scybalous stool, despite taking three Alophen pills each day. Usually two pills resulted in three movements a day. Three days before admission his physician noticed that he was icteric. He had experienced no pain, weight loss, anorexia or weakness. He became quite short of breath on climbing a long flight of stairs and had occasional cramp-like pains in the calves and feet. He had recently noticed difficulty in starting to urinate. Until the present illness he had always been active and well.

His wife and five children were in good health.

Physical examination revealed a mildly icteric man, with a moderately severe right scoliosis. He had varicose veins, as well as telangiectatic vessels over the legs and feet. The breath sounds were diminished over the right chest posteriorly. The heart was normal, and the pulse strong. The liver edge was felt well below the level of the umbilicus, even to the left of the midline. The left lobe of the liver was enlarged, as indicated by percussion over the posterior chest wall, and the spleen was not felt; the abdomen was otherwise negative. A large fairly smooth prostate was palpated.

The temperature, pulse and respirations were normal. The blood pressure was 165 systolic, 90 diastolic.

Examination of the blood showed a red-cell count of 5,600,000 and a white-cell count of 12,400, with 82 per cent neutrophils. The stool was formed, dark and guaiac negative. The urine was acid, with a specific gravity of 1.020, and gave a + test for albumin, a ++++ test for bile and a green precipitate with Benedict's solution; it contained 30 white cells per high-power field and showed a posi-

tive urobilinogen test in a dilution of 1:512. The serum nonprotein nitrogen was 125 mg. per 100 cc., the cholesterol 192 mg. and the phosphorus 4.2 mg. The total protein was 5.78 gm. per 100 cc., with an albumin-globulin ratio of 1.8. The van den Bergh test was 10.6 mg. direct and 13.6 mg. indirect, the cephalin flocculation test + + + +, the alkaline phosphatase 11.5 Bodansky units per 100 cc., and the prothrombin time 19 seconds (normal, 18 to 20 seconds).

An electrocardiogram showed a normal tracing. X-ray examination revealed a marked right dorsal scoliosis. The right diaphragm was somewhat elevated. Several linear areas of increased density were seen in the right lower lung field. The aorta was tortuous and calcified in the arch. The heart was not remarkable. By fluoroscopy the liver appeared enlarged.

On the third hospital day the patient became progressively more stuporous, responding only to pain. The temperature rose to 100.5°F. The pulse and respirations became moderately elevated. He became comatose and expired quietly on the fourth hospital day.

### DIFFERENTIAL DIAGNOSIS

DR. MARIAN W. ROPES: It is apparent that this patient had severe liver-cell damage, and I believe that his death was due to hepatic failure.

The disease, in so far as he was aware of it, was of short duration, a total of three and a half weeks, and there was some evidence in the laboratory studies to indicate that the acute liver damage was also of rather short duration. For instance, in severe liver-cell damage a prothrombin time of 19 seconds—a perfectly normal reading—is unusual if such damage has persisted for a long period of time. Similarly, in liver failure of considerable duration a normal cholesterol level is a somewhat unusual finding, a low reading usually being expected. If there is an obstructive element, an elevation on this basis might balance the lowering due to parenchymatous damage. I am sure, however, that this differential is not reliable. Furthermore, in liver damage of long duration one expects more of a decrease in the serum albumin and an elevation of the globulin. The other tests give adequate evidence of liver-cell damage—the high urobilinogen, the + + + + cephalin flocculation test, the high van den Bergh values and the high nonprotein nitrogen. I assume that the increase in nonprotein nitrogen was due to an increase in amino acids,—the usual finding in cases of hepatic failure,—and I suspect that the urea was only slightly elevated. There is little or no evidence of renal failure. The phosphatase level is somewhat higher than one would ordinarily expect in parenchymatous liver damage of short duration and suggests a slight element of obstruction, as does, theoretically, the high direct-indirect ratio in the van den Bergh test. Obviously

\*On leave of absence.

if any obstruction was present, it was relatively minimal compared to the parenchymatous damage.

One must next consider what caused this damage. Probably the most significant factor is the large size of the liver. May we look at the x-ray films?

DR. MILFORD D. SCHULZ: You can see this great mass filling the entire epigastrium. If it is not liver, it cannot be distinguished from it. The diaphragm is somewhat elevated. What this airless area in the right lung field is, I cannot say.

DR. ROPES: Assuming that the mass is liver, there surely is no question that it is tremendous.

DR. SCHULZ: I agree.

DR. ROPES: The first problem to be considered is whether an acute liver disease, such as acute infectious hepatitis, can produce this picture. Against that is the size of the liver; it being extremely unusual to observe a liver of this size at any stage of acute hepatitis, particularly at a terminal stage, when acute failure and death are imminent. Similarly, I should expect the spleen to be palpable in a hepatitis of this degree.

There are two other acute liver diseases that should be mentioned in passing. Thus, acute liver poisoning from any source might be considered on the basis of the history, but the large liver and the lack of further details permit us to discard this cause. Similarly there is no evidence for an infectious process, such as Weil's disease. So the evidence, to me, indicates underlying liver disease in which there was final failure of the remaining liver cells due to some superimposed factor.

There are three possibilities to consider: syphilis, a malignant tumor and cirrhosis. Unfortunately we are not told anything about the Hinton and Wassermann tests. The size of the liver, particularly that of the left lobe, demonstrated by a test that Dr. Aub will perhaps mention later, namely, posterior chest percussion, is entirely consistent with syphilis. Although syphilis cannot be ruled out, it also cannot be proved in this case.

A malignant neoplasm, either primary or secondary, must be considered. If it were metastatic carcinoma, it would be unusual to have so few symptoms, including absence of weight loss, up to three and a half weeks before death. Also there is no evidence of a primary source. Constipation came on during the last few weeks of life, and I interpret this as being secondary to hepatic failure rather than indicating a lesion of the gastrointestinal tract. I do not believe that the patient had prostatic carcinoma. If a malignant tumor was the etiologic factor, the course is more consistent with a primary carcinoma of the liver than with a metastatic lesion.

The third possibility is portal cirrhosis. There is no evidence of the biliary type from either the history or the laboratory findings. It is possible, although unlikely, for portal cirrhosis to cause a liver of this size, with left lobe enlargement. The absence of symptoms up to the terminal event, with failure

of the residual liver cells, is not inconsistent. I think again, however, that the relatively slight change in some of the chemical findings would be unusual in a cirrhosis of this duration and degree. Also, I should have expected more in the way of anemia, splenic enlargement and further evidence of portal-vein obstruction.

In addition there were arteriosclerosis, prostatic hypertrophy and something in the right lower chest that may have been atelectasis secondary to the liver enlargement. I doubt that this was related to the primary process in any other way.

To summarize I think that this man died because of hepatic failure and that he had underlying liver disease before the final terminal damage of the remaining liver cells. I favor a malignant tumor, although it is absolutely impossible to rule out syphilis.

DR. BENJAMIN CASTLEMAN: Do you want to go any farther in classifying the tumor?

DR. ROPES: I believe that it was a liver-cell carcinoma.

DR. JOSEPH C. AUB: I thought that this man had a primary tumor in the liver on the basis of hepatoma. I have always believed that these usually occurred in the left lobe of the liver, although Dr. Castleman disagrees with me.

Dr. Ropes has asked me to demonstrate one way of pointing out the size of the left lobe of the liver. One should percuss down just to the left of the spine until one comes to flatness; having come to flatness, one should percuss out laterally to resonance. This is a sharp line that should be 5 cm. from the midline in a normal person. With a big left lobe of the liver, it may measure 8 or 9 cm. The reason for this is that, the left lobe of the liver being in the back just behind the stomach, resonance develops when the liver edge ends and the gas bubble in the cardiac end of the stomach begins. This gives a quite accurate indication of left-lobe enlargement.

DR. CASTLEMAN: In our experience hepatomas are more frequent in the right lobe than in the left; when the left lobe is enlarged, we think oftener of syphilis than of primary tumor.

DR. CHESTER M. JONES: I am interested in the emphasis that Dr. Ropes has put on syphilis, since I would not have seriously thought of it. The liver was very large by the x-ray films and on physical examination, indicating a diffuse process, which I suppose would be called a cirrhosis. In a syphilitic process I believe that the physical findings are different — the mass is lobular.

In this case I thought immediately of primary hepatoma. Furthermore, primary hepatoma, or even metastatic cancer of the liver, may go for a long period of time without producing many symptoms or much interference with liver function, except when superimposed on cirrhosis. There is a difference in statistical figures, if one compares what we see here with what they see on the West Coast.

Wilbur, Wood and Willett\* report primary hepatoma without cirrhosis in a high percentage of cases; our cases are usually superimposed on cirrhosis.

DR. CASTLEMAN: About 90 per cent of our cases are associated with cirrhosis.

DR. JONES: There is an end picture of hepatic failure, as this patient exhibited, in any form of diffuse liver disease. In the final stage it is essentially the same clinical picture, regardless of whether the failure is due to acute yellow atrophy, infection, a specific toxin or any other cause. Incidentally, I should think that one would have found an enlarged spleen if this were a syphilitic cirrhosis, just as in any other form of cirrhosis.

DR. CASTLEMAN: For a syphilitic liver to be as big as this one was it would have to be the hepar lobatum type, which as a rule does not lead to liver failure unless acute hepatitis of some sort is superimposed. Acquired diffuse syphilitic cirrhosis is extremely rare, and I doubt that the liver would be so large.

#### CLINICAL DIAGNOSIS

Liver-cell carcinoma.

#### DR. ROPES'S DIAGNOSES

Liver-cell carcinoma.

Arteriosclerosis.

Pulmonary atelectasis: right lower lobe.

Prostatic hypertrophy.

#### ANATOMICAL DIAGNOSES

Malignant lymphoma, lymphoblastic type, involving liver, mesenteric and retroperitoneal lymph nodes and vertebral bone marrow.

Arteriosclerosis.

Pulmonary fibrosis and emphysema: right lower lobe.

Prostatic hyperplasia.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy the liver weighed 5000 gm., a tremendous liver. We do not usually see livers of that size, and when we do, they are almost always due to metastatic carcinoma. We have one liver of this size due to so-called "Hanot's cirrhosis," that is, a biliary type of cirrhosis. I believe that we had one or two almost that size during the extreme fatty stage of acute alcoholic hepatitis before the onset of fibrosis.

The liver was infiltrated with grayish-white, obviously neoplastic tissue, and we assumed that it was metastatic carcinoma. The mesenteric and retroperitoneal nodes were also involved, but we were unable to find the primary site. Microscopic examination showed why we did not find it. The tumor proved to belong to the malignant-lymphoma group. Most of the liver cells were completely re-

placed by cells of the lymphocytic series, predominantly lymphoblasts. There was no cirrhosis. Except for the mesenteric and retroperitoneal lymph nodes, which were replaced by neoplasm, the only other organ involved was the vertebral bone marrow.

The prostate was enlarged and showed hyperplasia. The abnormal x-ray shadow in the chest proved to have been due to fibrosis of the lungs with large emphysematous blebs in the right lower lobe.

#### CASE 31192

#### PRESENTATION OF CASE

A fifty-three-year-old engineer was admitted to the hospital because of mental confusion and severe headache of approximately twenty hours' duration.

Five years before entry he passed an examination for life insurance. The patient had been well and active until one year before admission, when he began having severe headaches at night, and was found to have a systolic blood pressure of 225 and albuminuria. Despite severe headaches he continued to work. At noon on the day before admission the patient had some teeth extracted. The oral surgeon reported that the patient did not look well and appeared somewhat confused. Two hours later the patient telephoned his wife and complained of pain in the jaw. Three hours later he called her again and told her that he was extremely sick. In the meantime his automobile was found in a badly wrecked condition. When the patient was found, it was observed that he had a small bruise on his forehead. He had no recollection of an accident, but he did recall wandering about the city, in the early afternoon, constantly bumping into people and being unable to find his office. At home that evening he spoke incoherently and appeared to be blind. During the night he complained of headache and was able to get up and go to the bathroom twice. On the following morning he was brought to the hospital.

Physical examination revealed a well-developed, poorly nourished, pale, sweating, extremely drowsy man who complained of a throbbing frontal headache. There was a small bruise on the forehead. The alveolar sockets were bleeding. All but the canine teeth had recently been extracted. The heart border was 8.5 cm. to the left of the mid-sternum in the fifth interspace. The sounds were distant and of poor quality. There were frequent extrasystoles. A systolic murmur was best heard at the apex. The dorsalis pedis arteries were easily felt. There was diminished visual acuity, with a left homonymous hemianopsia. Fundoscopy showed choked disks, retinal hemorrhages and spasm of the arteries, with marked bilateral arteriovenous nicking. There was a left lower facial weakness, but no weakness of arm or leg was detected. The

\*Wilbur, D. L., Wood, D. A., and Willett, F. M. Primary carcinoma of liver. *Ann. Int. Med.* 20:453-485, 1944.

neck was moderately stiff. There was a bilateral Kernig's sign. The left knee jerk was more prominent than the right. The abdominal reflexes were absent on the left. There was a questionable extensor plantar reflex on the left side.

The rectal temperature was 100°F., the pulse 105, and the respirations 10. The blood pressure was 220 systolic, 120 diastolic.

The urine was slightly alkaline, with a specific gravity of 1.014, and gave a +++ test for albumin; the sediment showed 10 to 15 white cells, 8 to 10 red cells and 3 granular casts per high-power field. Examination of the blood revealed a red-cell count of 4,200,000 and a white-cell count of 20,600, with 88 per cent neutrophils. The stool appeared normal and was guaiac negative. The serum non-protein nitrogen was 40 mg. per 100 cc., the protein 8 gm., and the carbon dioxide 29 milliequiv. per liter. A lumbar puncture gave an initial pressure equivalent to 300 mm. of water. All three tubes appeared equally "bloody," and the fluid contained 5850 red cells and 3 lymphocytes per cubic millimeter, but no polymorphonuclears; the supernatant fluid was xanthochromic. A spinal-fluid Wassermann test was negative, and the total protein was 129 mg. per 100 cc. The patient's headache was improved following the lumbar puncture. A lumbar puncture on the second day revealed an initial pressure equivalent to 350 mm. of water; there were 7800 red cells, 1400 polymorphonuclears and 700 lymphocytes per cubic millimeter, but no organisms were seen on smear. Cultures of the spinal fluid, urine and blood showed no growth.

An x-ray examination of the skull was negative. The pineal gland was calcified and not displaced. A chest film showed the heart to be prominent in the region of the left ventricle. The aorta was tortuous. There was evidence of healed pulmonary tuberculosis.

An electroencephalogram was grossly abnormal; the high-voltage, slow activity that constituted this abnormality appeared to be strongest in the anterior half of the head and was symmetrical except in the occiput where it was more marked on the left than on the right.

On the second day the patient was drowsier and more disoriented. No petechiae were seen. The temperature and pulse remained unchanged, and the respirations were about 20. The blood pressure varied from 220 systolic, 120 diastolic, to 240 systolic, 140 diastolic. The heart border was found by several examiners to lie 12 cm. from the midsternum in the fifth interspace. The pulmonic second sound was slightly greater than the aortic. The lungs were clear. The edge of the liver was felt two finger-breadths below the costal margin. There was no edema or dyspnea. The neurologic examination showed no change except for absent abdominal and cremasteric reflexes and increased rigidity of the neck. There was right horizontal nystagmus.

The extraocular muscles were normal, and the pupils reacted normally to light. The ophthalmoscopic findings were unchanged.

On the third hospital day the patient suddenly began to gasp, became unconscious and cyanotic and, within a few minutes, expired.

#### DIFFERENTIAL DIAGNOSIS

DR. MADELAINE R. BROWN: This is a remarkable case history and if I miss the diagnosis, it certainly will be my own fault. When I first read this record, it seemed to me to indicate a straightforward case of cerebral hemorrhage. After reading it a second time I began to see a few other things and it did not seem quite so simple.

We should consider several diagnoses. There are two that I need only mention. Brain tumor, such as angioma, may cause bleeding into the cerebrospinal fluid, but the onset here was sudden and the x-ray films showed that the pineal gland was in the midline; I think it unlikely that there was a tumor. The second diagnosis that needs mention is cerebral laceration. The patient bumped his head, but he had no fracture of the skull and I doubt that the blood was coming from a cerebral laceration. The conditions that we have to consider more seriously are a subarachnoid hemorrhage due to a ruptured aneurysm, a subdural hematoma and a cerebrovascular accident — either embolus, thrombosis or hemorrhage.

If we go back and attempt to reconstruct the story, the stage was set for a cerebrovascular accident. He had had hypertension for at least a year and possibly longer. He probably had cerebral arteriosclerosis and arteriosclerotic kidneys, and we know that he had retinal arteriosclerosis. He went to the dentist and had several teeth removed. Following this operation the dentist noticed that the patient was confused. Before the onset of a cerebral hemorrhage it is common for patients to complain of mental confusion, dizziness and headache. This patient knew that something was wrong and complained to his wife over the telephone that his jaw ached. He got into his car and started to drive, presumably to the office. He had an accident, probably because he lost consciousness. At least he remembered nothing about it, and the car was rather badly damaged. He escaped without any visible signs except a small bruise on the forehead. He got out of the car and started to wander around the city, although I do not know why he was allowed to. Apparently he bumped into people all the way because of his hemianopsia and could not find his office. Since he was able to walk, he had no hemiplegia, but he was confused and had a terrific headache. He again called his wife and said that he felt extremely ill. When he arrived home he was drowsy and confused but was well enough to get up and go to the bathroom that night. He still had no weakness

of the left side, but his headache became worse; he became more confused and finally was brought to the hospital. The next morning he had a stiff neck, bilateral Kernig signs, evidence of mental confusion and a spinal fluid that contained a great deal of blood.

If we try to localize this lesion before we discuss the nature of it, the electroencephalogram is not helpful. We have to depend on the clinical findings, and since all the signs are on the left, we must assume that the lesion was on the right side. What part of the right side? The hemianopsia seems to have been the most marked sign. Without hemiplegia or hemianesthesia we have to place the lesion in the occipital lobe, which indicates hemorrhage from the posterior cerebral artery and is rare. The most frequent source of cerebral hemorrhage is, of course, one of the short branches of the middle cerebral artery; the next is one of the long branches of the middle cerebral, then the anterior cerebral, the posterior cerebral and, finally, the basilar artery.

If we choose the posterior cerebral artery, even if it is an unusual site of hemorrhage, there are other signs for which we have to account — the weakness of the face, the questionable extensor plantar response, the hyperactive reflexes and absent abdominal reflexes on the left. So it seems to me that we have to make a diagnosis of two lesions: the second might have involved a small branch of the middle cerebral artery, supplying the right anterior central gyrus, or was possibly something outside the brain, such as a subdural hematoma.

If we place the chief lesion in the occipital lobe, what was its nature? Could there have been a subdural hematoma or ruptured aneurysm in the occipital area? Could there have been embolism or thrombosis rather than hemorrhage? It is possible that he had a subdural hematoma. He had an accident, and we know that people with arteriosclerosis are more susceptible to subdural hematoma than are those with normal vessels. But apparently the bruise on the forehead was a minor one. With a contrecoup effect one would expect involvement of the occipital region of the brain. It is possible, but not likely, that a recent subdural hematoma caused the blood in the spinal fluid, but it would not have caused the increased white-cell count, which usually comes from a rupture into the ventricle.

So far as aneurysm is concerned, certainly the homonymous hemianopsia is not typical of a ruptured aneurysm. Aneurysms of the cerebral vessels usually occur around the circle of Willis or at the beginning of the middle cerebral artery. It is possible that the mild hemiplegia was due to a ruptured aneurysm, but not the homonymous hemianopsia. So I do not believe that a ruptured aneurysm is likely.

Last of all we must consider the various kinds of vascular accidents. The chief lesion must have been a hemorrhage to account for the blood and white

corpuscles in the spinal fluid. There may have been a secondary lesion in the low parietal area to account for the weakness of the face, and that might have been an embolus in a small branch of the middle cerebral artery, following extraction of the teeth — an infected embolus. Or it might have been another small hemorrhage, but that is difficult to say.

I shall close with the following diagnoses: generalized arteriosclerosis, particularly retinal, cerebral and renal; hypertensive heart disease; hemorrhage into the right occipital lobe, with rupture into the ventricle; and possibly an embolus in a small branch of the right middle cerebral artery.

DR. JOST MICHELSEN: How do you account for the retinal hemorrhages?

DR. BROWN: Simply by the increased intracranial pressure, which was equivalent to 300 mm. of water. He may have had a subdural hematoma in addition to account for such an increase in pressure, but it does occur only with hemorrhage.

DR. FRANCIS M. RACKEMANN: Is not the story of the slow development of symptoms against severe hemorrhage?

DR. BROWN: Patients with severe cerebral hemorrhage generally do not have a sudden exitus. They usually last about as long as this patient did — from twenty-four hours to three days.

#### CLINICAL DIAGNOSIS

Cerebral hemorrhage.

#### DR. BROWN'S DIAGNOSES

Cerebral hemorrhage, right occipital region, with rupture into ventricle.  
Embolus, branch of right middle cerebral artery?  
Generalized arteriosclerosis.

#### ANATOMICAL DIAGNOSES

Cerebral hemorrhage, right posterior parietal region.  
Dissecting aneurysm of aorta, with rupture into pericardium.  
Cardiac hypertrophy, hypertensive type.  
Generalized arteriosclerosis.

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Before I call on Dr. Kubik to tell what was found in the brain I shall describe what was found in the heart.

This man was a hypertensive. He had a large heart, which weighed 500 gm. In the aorta just above the aortic valve was an intimal tear that had produced a dissecting aneurysm in the aorta as far as the arch, where it stopped (Fig. 1). This is quite unusual, for it is customary for a dissecting aneurysm to continue down the aorta into the abdominal portion and into the iliac vessels. This one stopped at the orifice of the right innominate artery, below which there was another intimal tear communicating with the aneurysm. There was an external rup-

ture through the adventitia at about the level of the proximal tear, so that there was a hemopericardium, which was the cause of the sudden exitus. This unusual condition could not have been suspected clinically.

DR. CHARLES S. KUBIK: There was moderate to

into the lateral ventricle, but the ependyma of the inferior horn was blood stained, indicating that there had been some leakage, which unquestionably accounted for the bloody spinal fluid. Although cerebral hemorrhage may occur in practically any part of the brain, including the cerebellum, it is



FIGURE 1.

marked arteriosclerosis, affecting particularly the basilar artery. There were small cerebellar and right temporal pressure cones. The right cerebral hemisphere was considerably enlarged because of a massive hemorrhage, 6 cm. in diameter, in the right posterior parietal region. There was no rupture

unusual in the posterior parietal or occipital regions. The most frequent site is the region of the lenticular nucleus, and the next, the pons, whereas a small number are scattered about in different places.

DR. CASTLEMAN: It is interesting to speculate whether the accident had anything to do with the

of the left side, but his headache became worse; he became more confused and finally was brought to the hospital. The next morning he had a stiff neck, bilateral Kernig signs, evidence of mental confusion and a spinal fluid that contained a great deal of blood.

If we try to localize this lesion before we discuss the nature of it, the electroencephalogram is not helpful. We have to depend on the clinical findings, and since all the signs are on the left, we must assume that the lesion was on the right side. What part of the right side? The hemianopsia seems to have been the most marked sign. Without hemiplegia or hemianesthesia we have to place the lesion in the occipital lobe, which indicates hemorrhage from the posterior cerebral artery and is rare. The most frequent source of cerebral hemorrhage is, of course, one of the short branches of the middle cerebral artery; the next is one of the long branches of the middle cerebral, then the anterior cerebral, the posterior cerebral and, finally, the basilar artery.

If we choose the posterior cerebral artery, even if it is an unusual site of hemorrhage, there are other signs for which we have to account — the weakness of the face, the questionable extensor plantar response, the hyperactive reflexes and absent abdominal reflexes on the left. So it seems to me that we have to make a diagnosis of two lesions: the second might have involved a small branch of the middle cerebral artery, supplying the right anterior central gyrus, or was possibly something outside the brain, such as a subdural hematoma.

If we place the chief lesion in the occipital lobe, what was its nature? Could there have been a subdural hematoma or ruptured aneurysm in the occipital area? Could there have been embolism or thrombosis rather than hemorrhage? It is possible that he had a subdural hematoma. He had an accident, and we know that people with arteriosclerosis are more susceptible to subdural hematoma than are those with normal vessels. But apparently the bruise on the forehead was a minor one. With a contrecoup effect one would expect involvement of the occipital region of the brain. It is possible, but not likely, that a recent subdural hematoma caused the blood in the spinal fluid, but it would not have caused the increased white-cell count, which usually comes from a rupture into the ventricle.

So far as aneurysm is concerned, certainly the homonymous hemianopsia is not typical of a ruptured aneurysm. Aneurysms of the cerebral vessels usually occur around the circle of Willis or at the beginning of the middle cerebral artery. It is possible that the mild hemiplegia was due to a ruptured aneurysm, but not the homonymous hemianopsia. So I do not believe that a ruptured aneurysm is likely.

Last of all we must consider the various kinds of vascular accidents. The chief lesion must have been a hemorrhage to account for the blood and white

corpuscles in the spinal fluid. There may have been a secondary lesion in the low parietal area to account for the weakness of the face, and that might have been an embolus in a small branch of the middle cerebral artery, following extraction of the teeth — an infected embolus. Or it might have been another small hemorrhage, but that is difficult to say.

I shall close with the following diagnoses: generalized arteriosclerosis, particularly retinal, cerebral and renal; hypertensive heart disease; hemorrhage into the right occipital lobe, with rupture into the ventricle; and possibly an embolus in a small branch of the right middle cerebral artery.

DR. JOST MICHELSEN: How do you account for the retinal hemorrhages?

DR. BROWN: Simply by the increased intracranial pressure, which was equivalent to 300 mm. of water. He may have had a subdural hematoma in addition to account for such an increase in pressure, but it does occur only with hemorrhage.

DR. FRANCIS M. RACKEMANN: Is not the story of the slow development of symptoms against severe hemorrhage?

DR. BROWN: Patients with severe cerebral hemorrhage generally do not have a sudden exitus. They usually last about as long as this patient did — from twenty-four hours to three days.

#### CLINICAL DIAGNOSIS

Cerebral hemorrhage.

#### DR. BROWN'S DIAGNOSES

Cerebral hemorrhage, right occipital region, with rupture into ventricle.

Embolus, branch of right middle cerebral artery?

Generalized arteriosclerosis.

#### ANATOMICAL DIAGNOSES

Cerebral hemorrhage, right posterior parietal region.

Dissecting aneurysm of aorta, with rupture into pericardium.

Cardiac hypertrophy, hypertensive type.

Generalized arteriosclerosis.

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Before I call on Dr. Kubik to tell what was found in the brain I shall describe what was found in the heart.

This man was a hypertensive. He had a large heart, which weighed 500 gm. In the aorta just above the aortic valve was an intimal tear that had produced a dissecting aneurysm in the aorta as far as the arch, where it stopped (Fig. 1). This is quite unusual, for it is customary for a dissecting aneurysm to continue down the aorta into the abdominal portion and into the iliac vessels. This one stopped at the orifice of the right innominate artery, below which there was another intimal tear communicating with the aneurysm. There was an external rup-

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## PSYCHOSOMATICS

WHEN, in 1822, William Beaumont, a native of Lebanon, Connecticut, exercised his Yankee ingenuity by holding a pannikin under Saint Martin's gastric fistula and catching the drippings, he was selling the world no wooden nutmeg. He was anticipating the work that Pavlov would do later with considerable refinement in technic, — Pavlov, for instance, early abandoned the use of gunfire in producing his fistulas, — and he was paving the way for the conclusions that Cannon would arrive at somewhat later on the bodily changes in pain, hunger, fear and the various subsidiary emotions.

Beaumont, in other words, laid the groundwork for a scientific approach to the study of mind and matter, and the influence of the former over the latter — a reality empirically accepted and never for an instant doubted by Bishop Berkeley, the homeopaths, the mesmerists, Elisha Perkins and the followers of Mary Baker Eddy.

Except for a few ardent and credulous cults, however, and a numerically less imposing group of psychologically and scientifically minded physicians, it has required for the population at large a second world war and a popular pictorial magazine to acquaint them with the actuality of psychosomatics.

It is time for the public to tire of chasing vitamins, as a cat chases its tail, having it always with him but never catching up with it — the matter of vitamins was practically settled, as we are beginning to learn, with the discovery of food. But the psychic origin of peptic ulcer is something new over which to agonize, and the thought that a cold in the head, an attack of asthma or a cardiovascular crisis may have its inception in the imagination is, for many, a novel idea with which to toy.

We had not, as a matter of fact, entirely failed to realize that an appreciation of the power of the intellect over our more earthy functions is no new idea, regardless of the enthusiasm of the neopsychosomatists. John Hunter proclaimed his life to be in the hands of any man who dared annoy him; followers of the cult of voodoo will lay themselves down and die if they so much as think that the witch doctors are after them; and a combat soldier in any war has known that no intestinal pathogen is necessary to produce an attack of uncontrollable diarrhea. Any radio listener, indeed, who has been unable to avoid suffering at the sound of a warbled commercial plug while waiting for his favorite commentator knows how these silly symphonies of the air may inspire in some of their hearers feelings of the blackest melancholy and, in others, those of incipient nausea.

It is something to be aware of the psychic stimuli that can erupt at the somatic level; when we can control them we may indeed know the peace that passeth understanding.



dissecting aneurysm. We know that occasionally a dissecting aneurysm results from trauma. If this were so, there should have been evidence of trauma to the chest, which was lacking. The aorta did show medial degeneration or what is called "media necrosis cystica," which predisposes the aorta to the development of a dissecting aneurysm. I suppose that the symptoms that he might have had

because of the aneurysm were masked by those of the cerebral hemorrhage.

DR. KUBIK: How old was the dissecting aneurysm?

DR. CASTLEMAN: Just a matter of a few days. The blood in the dissecting aneurysm was rather fresh, not the organized clot that one usually sees in an old dissecting aneurysm.

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## HODGKIN'S DISEASE\*

### IV. Involvement of Certain Organs

HENRY JACKSON, JR., M.D.,† AND FREDERIC PARKER, JR., M.D.‡

BOSTON

IN THIS article the involvement of certain organs will be discussed.

#### HILAR NODES AND MEDIASTINAL TUMOR

##### *Hodgkin's Paragranuloma*

As has already been noted, involvement of the mediastinal lymph nodes occasionally occurs in Hodgkin's paragranuloma, and from the limited series of cases that have been under our observation, such involvement does not appear to alter the prognosis. Massive mediastinal tumors do not occur.

##### *Hodgkin's Granuloma*

It is a frequent event in Hodgkin's granuloma to find enlargement of the hilar nodes or the development of a large mediastinal tumor (Figs. 1 and 2). Peirce,<sup>1</sup> not all of whose cases were subjected to biopsy or autopsy, found in an exhaustive study of 198 cases that 38 per cent had either intrathoracic tumor or adenopathy, and he wisely noted that the roentgenographic evidence of such lesions was far greater than the clinical signs or symptoms of intrathoracic abnormality indicated.

Of 174 cases that were carefully followed at the Pondville Hospital or the Collis P. Huntington Memorial Hospital, 90 (52 per cent) had enlargement of either the hilar or mediastinal nodes, and in 26 of these the mass was sufficiently large to be dignified by the adjective "massive," for it involved at one time or another, well over half the diameter of the chest. In general, involvement of these nodes may be found at any time of life, although there is a tendency for the more massive tumors to develop in patients under thirty years of age.

Implication of the mediastinal and hilar nodes, although usually an early accompaniment of Hodg-

kin's granuloma, may occur at any time during the course of the disease. In 36 per cent of 90 cases in the present series with mediastinal involvement, it was found simultaneously with the apparent onset of the condition; in another 38 per cent, it appeared within less than a year; and in but 13 per cent had the fundamental disorder been outwardly manifest for over three years before the development of the mediastinal tumor. Such facts indicate clearly the necessity for roentgen-ray study of the chest when the patient is first seen, even though there are no symptoms or signs even remotely suggesting such lesions.

It is noteworthy that in but 1 case was there evidence during life of an intrathoracic mass without coincident or antecedent peripheral lymphadenopathy. This fact should be of considerable value in the differential diagnosis of mediastinal Hodgkin's granuloma from aneurysm of the aorta and from benign tumors amenable to surgical removal, and indicates the wisdom of searching with meticulous care for enlarged lymph nodes, especially in the neck and axillas, in the presence of mediastinal tumor.

In the case of a forty-three-year-old man who died of lobar pneumonia, autopsy showed involvement of the para-aortic and peribronchial lymph nodes without the slightest evidence of Hodgkin's granuloma elsewhere. The diseased nodes were markedly sclerotic and showed evidence of spontaneous healing. This case indicates the possibility of primary involvement of the mediastinum, and we have previously pointed out in the discussion of the pathological aspects of the disease that primary mediastinal involvement appeared in 9 of the autopsied cases.

The symptoms or signs that may properly be attributed to involvement of the mediastinum are summarized in Table 1. It will be seen that dyspnea, occasionally extreme, and cough, often harassing and persistent, were the most frequent symptoms. Pleural effusion, clubbing of the fingers and cyanosis were the most frequent signs, but it was not always

\*From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard) and the Mallory Institute of Pathology, Boston City Hospital, the Department of Medicine, Harvard Medical School, and the Pondville Hospital, Massachusetts Department of Public Health.

†This is the fourth of a series of seven papers covering the various aspects of Hodgkin's disease.

‡Assistant professor of medicine, Harvard Medical School, associate physician, Thorndike Memorial Laboratory, Boston City Hospital, physician, Pondville Hospital, Wrentham, Massachusetts.

§Associate professor of pathology, Harvard Medical School, pathologist-in-chief, Boston City Hospital.

## SCARLET FEVER AND STREPTOCOCCAL SORE THROAT

SOME time ago the *Journal* called attention to the fact that the rules of isolation and quarantine now in force in many communities have not kept pace with present-day understanding of the epidemiology of certain infectious diseases.<sup>1</sup> This is particularly true with regard to scarlet fever, which has been singled out from the group of hemolytic streptococcus infections as the only one in which isolation and quarantine are required. Although patients with scarlet fever are quarantined for three or four weeks, there are no restrictions placed on cases of tonsillitis or pharyngitis, which may be equally important in spreading streptococcal infections, including scarlet fever.

An important step has recently been taken by the Department of Health of New York City in an attempt to remedy this situation. The provisions regarding scarlet fever have been changed in the latest revision of the Sanitary Code in that city to read as follows<sup>2</sup>:

1. The reportable disease scarlet fever is now included in a wider classification, namely, streptococcal sore throat, including scarlet fever.
2. The isolation period for streptococcal sore throat, including scarlet fever, is as follows:

*Uncomplicated case.* Until the mucous membrane of nose and throat appear normal, but for not less than seven days after onset of the disease.

*Complicated case* (discharging nose and ears, mastoids, enlarged or suppurating glands, pneumonia). Until recovery from the complicating condition, except that, if the complication persists for forty-five days from onset, two cultures not less than twenty-four hours apart may be taken, and if these are negative for *Streptococcus haemolyticus*, the case may be discharged. Such cultures must be submitted to and examined by the laboratory of the Department of Health

3. Contacts are not excluded from school or work.
4. Visits by nurses to the homes of cases of scarlet fever are no longer required.
5. Children recovered from streptococcal sore throat, including scarlet fever, may be readmitted to school on a card issued by the Department of Health or the Department of Hospitals, or on a signed statement of a physician certifying that the child has recovered.

There will probably be some objections to the wording of the new regulations. It also remains to be seen whether they can be carried out as readily and effectively as the older ones. Nevertheless, it appears to be a step in the right direction. The

efficacy of the older regulations in reducing the spread of infection has been seriously questioned and it will be interesting to see whether these changes will in any way affect the epidemiologic pattern of scarlet fever and hemolytic streptococcus infection in New York City.

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1. Editorial. Streptococcus sore throats and scarlet fever. *New E. J. Med.* 229:599, 1943.
2. Recent changes regarding scarlet fever. *Quart. Bull., Dept. of Hlth. City of New York* 13:1, 1945.

## MASSACHUSETTS MEDICAL SOCIETY DEATH

MOIR — Marguerite W. Moir, M.D., of Boston, died December 3, 1944. She was in her seventy-second year. Dr. Moir received her degree from Boston University School of Medicine in 1918.

## MISCELLANY PRIZE ESSAY

*Modern Hospital* has recently announced a competition for an essay on the subject "A Plan for Improving Hospital Treatment of Psychiatric Patients." Three prizes, totaling \$900, will be awarded by the judges, who will be drawn from the United States Public Health Service, the American Psychiatric Association and the National Committee on Mental Hygiene. The competition is open to anyone except the judges and the employees of *Modern Hospital*, and essays must be received by October 1, 1945. Further details may be obtained from the Modern Hospital Publishing Company, 919 North Michigan Avenue, Chicago 11.

## NOTICES

### ANNOUNCEMENTS

Dr. John B. Hall announces the removal of his office from 60 Windsor Street to 108 Dudley Street, Roxbury.

Dr. Savvas E. Theodore announces the removal of his office from 14 Chestnut Street, Springfield, to 510 Commonwealth Avenue, Boston.

## MEDICAL ART SHOW

*Modern Medicine's* Medical Art Show will open at Yale University School of Medicine in the Harvey Cushing Room on May 20 and will continue until June 3. Previous showings at Baltimore's Enoch Pratt Library, the Cleveland Health Museum, the Minneapolis Public Library, Rochester Rundel Memorial Building and the Brooklyn Public Library have attracted over 100,000 people. The work of the late Mr. Broedel, often called the father of medical art, together with that of many of the artists who studied with him in the School of Art as Applied to Medicine, which he founded at Johns Hopkins University School of Medicine, forms a large part of the exhibit. Included among the exhibitors is Miss Marie McLatchie, head of the school of illustration at the Massachusetts General Hospital. The collection has been assembled by *Modern Medicine* as a tribute to the American medical artist, too long unknown and unsung, and yet such a vital factor in recording all progress in medicine.

(Notices continued on page xxvii)



FIGURE 1 *Mediastinal Involvement before Treatment*

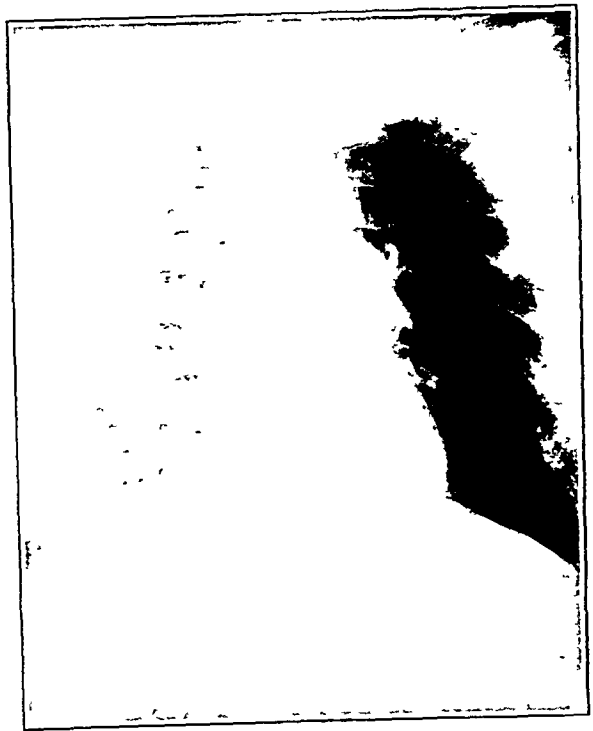


FIGURE 2 *The Same after Treatment.*



FIGURE 3. *Nodular Involvement of the Lung and Mediastinum.*



FIGURE 4 *Tuberculosis Associated with Hodgkin's Granuloma*

clear whether the mediastinal involvement was solely responsible, for in a considerable number of cases there was coincident involvement of the parenchyma of the lung; furthermore, some of the

TABLE 1. *Symptoms Referable to Enlarged Mediastinal Nodes in Ninety Cases of Hodgkin's Granuloma.*

SYMPTOM	No OF CASES
Dyspnea	48
Cough	47
Pleurisy with effusion	23
Serous	17
Sanguinous	5
Chylous	1
Clubbed fingers	8
Cyanosis	7
Hemoptysis	5
Enlarged superficial veins	4
Dysphagia	3
Hiccoughing	1
Hoarseness	1
No symptoms	18

symptoms listed may well have been due to concomitant pathologic lesions not necessarily located within the chest. We are forced to the conclusion that x-ray examination of the chest is not only wise but necessary.

It is especially noteworthy that pleurisy with effusion frequently accompanies mediastinal involvement. In such cases the attendant physician should not only remove the fluid but should subsequently search carefully for evidence of hilar or mediastinal nodes so that appropriate x-ray therapy may be instituted if necessary.

In certain cases, the mass can be outlined by percussion anteriorly or gives rise to D'Espine's sign posteriorly, but it is often difficult to detect even a large mediastinal tumor by physical signs alone. It is, furthermore, necessary to remember that early involvement of the hilar or mediastinal lymph nodes may be completely masked, in the frontal plane, by the normal shadow of the heart and great vessels. Lateral or oblique views capable of visualizing the anterior and posterior mediastinal spaces should therefore always be taken. Early there is only an increase in the hilar shadows. Later there is obliteration of the normal outlines of the supracardiac shadow or a blocking out of the normally aerated substernal or retrocardiac space. As the process extends still farther, there appears a homogeneous, dense shadow, usually bilateral, with outlines that as a rule are sharply demarcated from the surrounding lung parenchyma, although there may be direct involvement of the lung parenchyma as well, and although in certain cases atelectasis of part of a lobe — particularly the lower — is brought about.

In some cases, the contour of the tumor is that of a truncated cone; in others, the mass is irregularly lobulated, and more rarely semicircular shadows project from the hilar region. On the basis of the x-ray findings alone, it is often impossible to differentiate mediastinal Hodgkin's granuloma, bronchiogenic carcinoma and aneurysm of the aorta, and we have seen a case in which a cervical lymph node

showed on biopsy Hodgkin's granuloma, whereas autopsy showed a large bronchiogenic carcinoma close to the hilar region. Of considerable value in differentiating tumor from aneurysm is the fact that in the former there is frequently a homolateral elevation of the diaphragm, a sign rarely seen in the presence of an aortic aneurysm.

Erythema nodosum should also be borne in mind. We have seen several patients who had considerable enlargement of the mediastinal nodes due to this condition, and as the enlargement may persist for a long time after the skin lesions have disappeared, the diagnosis may be difficult.

The course of the disease does not appear to be materially altered by the presence of hilar or mediastinal nodes, which usually respond surprisingly well to radiation. Of the 90 patients with mediastinal involvement in this series, 80 have died, with an average duration of life of 2.7 years. The average duration in the 10 living patients is 4.7 years, and 1 patient is still in reasonably good health thirteen years after onset. In rare cases, however, the mediastinal tumor develops so fast and to such an extent that death rapidly ensues.

#### *Hodgkin's Sarcoma*

Involvement of the mediastinal lymph nodes occurs in approximately one third of the cases of Hodgkin's sarcoma and is not infrequently associated with an extension of the process into the lung. In none of the present cases was there mediastinal involvement without coincident peripheral lymphadenopathy. It is evident from Table 2 that the symp-

TABLE 2. *Symptoms Referable to Enlarged Mediastinal Nodes in Ten Cases of Hodgkin's Sarcoma.*

SYMPTOM	No OF CASES
Dyspnea and cough	7
Sanguinous pleural effusion	1
None	2

toms are few in comparison with those of mediastinal involvement in Hodgkin's granuloma.

All patients with mediastinal involvement were over thirty-five years of age. This age distribution does not differ in general from that of Hodgkin's sarcoma.

Mediastinal involvement usually occurs late in the course of the disease. Very rarely it is the initial sign.

The nodes are usually only slightly enlarged. Rarely there is massive involvement. In 1 case, the process extended into the lung, giving rise to dullness over the entire right lower lobe. In view of the fact that the patient was admitted with a high temperature and these signs, the case was initially mistaken for one of lobar pneumonia. In the second case, there was extension into the parenchyma of the lung, but the process was not extensive.

without involvement of the mediastinum. In contrast to Hodgkin's granuloma, pleurisy with effusion is notably rare; we have seen but 1 case in which this complication occurred, and in this the effusion was bloody.

### GASTROINTESTINAL TRACT

#### *Hodgkin's Paragranuloma*

Involvement of the gastrointestinal tract does not occur in this form of the disease.

#### *Hodgkin's Granuloma*

Gastrointestinal symptoms are frequent in Hodgkin's granuloma, but demonstrable lesions of the alimentary canal, either during life or at autopsy, are comparatively rare. Sherman<sup>5</sup> has reviewed the literature pertaining to this interesting aspect of the subject, and the reader is especially referred to his excellent paper and the earlier more detailed study of Coronini.<sup>6</sup> From many available articles it is difficult to be certain in many cases whether the lesions referred to are actually those of Hodgkin's granuloma. Hodgkin's sarcoma, lymphosarcoma or reticulum-cell sarcoma. In view of the fact that the incidence of gastrointestinal lesions as well as their treatment and prognosis differs according to the type of pathologic process present, this confusion is unfortunate yet readily understandable, for the histologic picture of lymphoma in the gastrointestinal tract is by no means so simple and definite as it usually is in the lymph nodes.

It seems clear, however, that Hodgkin's granuloma occasionally occurs as a primary and possibly as an isolated lesion of the alimentary canal and that secondary gastrointestinal lesions are found in the generalized disease, usually rather late in the course. There are few reliable statistics concerning the actual frequency of such lesions. Sternberg,<sup>7</sup> however, whose criteria for the diagnosis were clear-cut and definitive, found that in 52 autopsies the stomach was involved in 6 cases and the small intestine in 5. As already stated in the part of this article dealing with the pathological aspects of the disease, our experience is similar. Twenty-four of the 213 patients in this series had gastrointestinal symptoms at onset, yet only 9 of these could subsequently be shown to have any intrinsic lesion of the stomach or bowel. During the course of the disease such complaints are more frequent, and indeed they may for a time dominate the clinical picture. Anorexia, abdominal pain, nausea, vomiting and constipation — occasionally alternating with diarrhea — were the most frequent symptoms in 174 cases followed to date or death (Table 3).

Among all these patients exhibiting gastrointestinal symptoms late in their course, only 3 were shown during life to have actual intrinsic lesions of the alimentary canal. In 2 cases, the lesion was in the lower part of the large intestine and responded

well, at least for a time, to cautious x-ray therapy (Figs. 5 and 6). In the third case, the lesion was in the esophagus (Fig. 7), and there was poor response to radiation.

It is probable that such symptoms as loss of appetite, nausea and vomiting can be attributed to the general systemic effects of the disease, and all are likely to be temporarily aggravated by x-ray therapy, although often subsequently relieved by the same therapeutics. It is well to advise patients that this is so.

Abdominal pain seems to be caused in the majority of cases by enlarged lymph nodes pressing on sensory nerves. Dysphagia may be due either to pressure from a mediastinal tumor on the esophagus or to an intrinsic lesion of that structure. Extremely rarely, it is due to massive involvement of

TABLE 3. *Gastrointestinal Symptoms in 174 Cases of Hodgkin's Granuloma.*

Symptom	No of Cases
Anorexia	56
Abdominal pain	37
Nausea	27
Constipation	24
Vomiting	20
Diarrhea	7
Dysphagia . . .	4
Melena	2
Hematemesis	2

the tonsils by the granulomatous process. Hematemesis was directly traceable in 1 case to a widespread involvement of the stomach, but in 2 cases in which this symptom was a prominent feature, no gastrointestinal lesion could be demonstrated even after careful clinical study. It is possible that in such cases the vomiting of blood is secondary to the general hemorrhagic diathesis that is occasionally seen, particularly toward the end of the disease, or that the cause would have been found at autopsy. Similarly, melena was obviously caused by gastrointestinal lesions in 3 cases, yet in 2 cases in which this symptom appeared late in the disease no cause could be found during life.

In the 174 cases followed to date or to death, definite clinical evidence of lesions of the gastrointestinal tract was found in 9 cases (5 per cent). In 6 of these, the lesions proved at autopsy to be primary in the gastrointestinal tract and confined almost entirely to the viscus concerned and the immediately adjacent lymph nodes, so that there seems to be some justification for speaking of the gastrointestinal form of Hodgkin's granuloma. The stomach was involved in 3 cases, the cecum in 2, the sigmoid in 2, and the duodenum and esophagus each in 1.

It is to be noted that in no case was there multiple involvement of the gastrointestinal tract, although in a larger series, of course, such might well be true. In no case were these lesions suspected or demonstrated during life. The clinical importance of these post-mortem findings lies in the fact that such lesions may for some time be asymptomatic, yet the

It seems doubtful whether mediastinal involvement has any particular bearing on the prognosis of any given case.

## LUNGS

### *Hodgkin's Paragranuloma*

In Hodgkin's paragranuloma, involvement of the lung does not occur. Occasionally, however, there is implication of the mediastinal nodes, and the occurrence of such an event, as previously indicated, does not necessarily imply that the prognosis is poor.

### *Hodgkin's Granuloma*

Evidence of involvement of the lung is not infrequent during the course of Hodgkin's granuloma, and pulmonary lesions are found at autopsy with even greater frequency. Peirce,<sup>1</sup> in a careful study of 198 cases, in 85 per cent of which the diagnosis had been substantiated by biopsy or autopsy, found that 14 per cent showed roentgenologic evidence of parenchymal infiltration without pleural involvement and noted that the lesions might simulate acute inflammatory disease, pulmonary abscess, tuberculosis, primary carcinoma or metastatic neoplasm. In the present series of proved cases followed to date or to death, roentgenologic evidence of lung involvement was also found in 14 per cent. As already pointed out, pulmonary lesions are even more frequent at autopsy; in this series, there was involvement in 41 per cent.

Versé<sup>2</sup> has carefully reviewed the literature pertaining to this aspect of Hodgkin's disease, and concludes that the lung is involved either primarily or secondarily in approximately one third of all cases coming to autopsy. Enlargement of the mediastinal and hilar nodes may, furthermore, bring about partial or complete stenosis of the bronchi, with consequent pulmonary atelectasis, and the pulmonary signs or symptoms arising from such a sequence of events are not infrequently of greater import than those due to direct involvement of the lung. Moreover, it should be pointed out that not infrequently, under x-ray therapy, a mediastinal mass entirely disappears while the parenchymal lesions remain relatively unchanged.<sup>3</sup> It is possible that some of these so-called "parenchymatous lesions" are in reality small areas of atelectasis peripheral to obstruction of a small bronchus.

In very rare cases, necrosis of some magnitude develops so that cavities simulating those of tuberculosis or abscess are seen. Versé<sup>2</sup> cites 8 such cases; we ourselves have not seen this type of lesion.

Invasion of the lung may occur at any time during the course of the disease. Weber<sup>4</sup> describes the case of a seventy-three-year-old woman in whom a diagnosis of primary bronchiogenic carcinoma had been made on clinical grounds. Autopsy showed Hodg-

kin's granuloma involving the main bronchi on the left, together with a small portion of the adjacent lung tissue. No metastases, even in the hilar nodes, could be demonstrated. Versé<sup>2</sup> has collected from the literature and from his own material 10 cases in which the pathologic process was apparently primary in the lung or bronchi. Such cases are, however, admittedly extremely rare, and we have not seen any.

In our own series, pulmonary lesions were demonstrated by x-ray studies as early as one month after the apparent onset of the disease and as late as twelve years after it. It must be remembered, however, that unless routine x-ray studies are carried out at fairly frequent intervals, the precise time of the development of the parenchymal infiltration may be misjudged, for it is obvious that many of the symptoms and signs depend not on parenchymal involvement itself but rather on enlargement of hilar or mediastinal nodes.

The most frequent symptoms found in patients with parenchymal disease are dyspnea, cough and fever. More rarely the patient complains of pain in the chest. Hemoptysis is extremely unusual, and its presence should arouse one's suspicion of tuberculosis. Occasionally there are neither symptoms nor signs, — a fact that serves to emphasize the importance of routine x-ray examination of the chest, — and it is worth while to draw attention once more to the obvious fact that any of the signs and symptoms of parenchymal involvement may be occasioned by the presence of a mediastinal mass. Twenty per cent of patients showing pulmonary involvement have pleurisy with effusion. Only extremely rarely is this effusion bloody.

The x-ray picture of pulmonary Hodgkin's granuloma is in no sense pathognomonic. As has already been said, the picture may simulate acute inflammatory disease, pulmonary abscess, tuberculosis, primary bronchiogenic carcinoma or metastatic neoplasm<sup>1</sup> (Fig. 3), and it must be remembered that pulmonary tuberculosis is a not infrequent complication of Hodgkin's granuloma (Fig. 4).

### *Hodgkin's Sarcoma*

The lungs are involved in Hodgkin's sarcoma in approximately 28 per cent of the cases, or nearly twice as often as in Hodgkin's granuloma. In all cases, there were cough and dyspnea, which were frequently severe. Fever is not unusual, although it is rather unusual in Hodgkin's sarcoma as a whole, and chills are rarely seen. Conversely, the presence of persistent cough generally indicates that the parenchyma of the lung has been invaded. The pulmonary lesions may extend outward from the mediastinum or they may resemble patches of bronchopneumonia. Rarely there is massive involvement of an entire lobe.

Parenchymal involvement of the lung is usually associated with involvement of the mediastinal nodes. Much more rarely there are isolated areas

patient may die suddenly from a rupture of a gastric or intestinal granulomatous lesion. This event took place in 1 patient, who was discharged apparently in good condition but died six hours later from a ruptured large intestine.

Clinically, Hodgkin's granuloma of the gastro-intestinal tract most frequently simulates carcinoma, ulcerative colitis or enteritis, or obstruction of the bowel.<sup>5</sup> The majority of published cases have occurred in the fifth and sixth decades of life, and this was so in the present series.

Coincident enlargement of the superficial lymph nodes is said to be infrequent.<sup>5, 6</sup> One patient had what appeared on x-ray examination to be a carcinoma of the stomach. There was no peripheral lymphadenopathy. He was operated on later, and the stomach was found to be extensively involved with Hodgkin's granuloma.

With involvement of the stomach, the signs and symptoms do not differ materially from those of carcinoma, and epigastric pain, melena, loss of weight, hematemesis and vomiting are the most frequent ones. Rarely a mass is felt. Singer<sup>9</sup> believes that the disclosure at operation of a soft, flat, infiltrating tumor associated with isolated soft lymph nodes in the adjoining mesentery should arouse the suspicion of Hodgkin's disease. He adds, however, that for a final diagnosis the microscope is indispensable. With this we agree. Involvement of the intestine produces symptoms that are much the same, although abdominal pain and constipation are usually more prominent than they are with involvement of the stomach. Hemorrhage and perforation are rare but, as has been pointed out, may be fatal.

On x-ray examination, the findings again are usually those of carcinoma. A single case with an esophageal lesion illustrates this point.

E. J. (H 39-583), a 59-year-old man, was admitted to the hospital on May 8, 1939. The past and family histories were uneventful. In April, 3 weeks before entry, he noticed a lump above the right clavicle. This was removed at another hospital, and a microscopic diagnosis of Hodgkin's granuloma was made and confirmed by us later.

Physical examination on admission showed a well-developed and well-nourished man. No abnormalities of importance were found other than a few bean-sized lymph nodes in the right axilla. The laboratory findings were essentially normal. Deep x-ray therapy was given, with a total of 1000 r, divided between the right side of the neck and the right axilla, and within a few weeks the enlarged nodes had disappeared.

The patient remained symptom-free until December, when he began to complain of difficulty in swallowing. X-ray studies showed an extensive irregularity of the middle third of the esophagus (Fig. 7), and an esophagoscopy on January 10, 1940, showed a large, freely bleeding and obstructive neoplastic process at the junction of the middle and lower thirds. A biopsy taken at that time showed a lesion with the characteristic picture of Hodgkin's granuloma. After appropriate x-ray therapy no trace of the lesion could be found by x-ray studies. After several months, the patient died of unknown causes.

It is impossible to say with any degree of assurance whether the esophageal lesion was primary or secondary, although the latter seems the likelier. In

any event, it was the only lesion of the esophagus seen in the 174 cases of Hodgkin's granuloma.

In 2 cases, the gastric lesion involved the greater curvature. In a third case, there was tremendous dilatation of the stomach owing to an obstructive lesion at the pyloric area, an unusual finding in gastric carcinoma. In all there was marked reduction of the peristaltic waves over a wide area. In no case was there the convoluted appearance that has been said to be characteristic of lymphoma.

C. H. (BCH 828826), a 56-year-old woman, was admitted to the hospital on July 9, 1936. The past history was uneventful, except that she had had a chronic productive cough for many years. Two months before entry, she noticed considerable weakness and fatigue, and during the next few weeks she vomited on numerous occasions and lost much weight. For a week before admission, she had had fever and night sweats. There was no abdominal pain, anorexia, nausea, melena or hematemesis.

Physical examination showed an emaciated, rather drowsy woman. There was a harsh, rasping systolic murmur over the entire precordium, heard best at the apex and transmitted up the vessels of the neck. The heart was enlarged 2 cm. beyond the midclavicular line. There were dullness and moist rales at the bases of both lungs. In the right para-umbilical area was felt a small, irregular, firm mass that descended freely on respiration. Otherwise the physical examination revealed no abnormalities of importance.

The red-cell count was 2,750,000, the hemoglobin 46 per cent, and the white-cell count 4000 with 60 per cent segmented neutrophils, 21 per cent young neutrophils, 2 per cent eosinophils, 5 per cent lymphocytes, 5 per cent myelocytes and 4 per cent myeloblasts. The stools gave a strongly positive guaiac test.

The temperature was of the septic type, ranging each day from 99 in the morning to 103°F. at night. The respirations were normal. The pulse averaged 115.

X-ray films of the lungs showed congestion of both bases. Those of the gastrointestinal tract showed that the second portion of the duodenum was irregular and mottled in appearance, with a definite narrowing at the junction of the second and third portions. A diagnosis of carcinoma of the duodenum was made.

The patient continued to run a septic temperature, became increasingly drowsy and died less than a month after admission.

*Autopsy* (A 36-449). This showed Hodgkin's granuloma primary in the second and third portions of the duodenum, with extension to the immediately adjacent mesenteric lymph nodes. That portion of the jejunum immediately distal to the duodenum was necrotic, and it ruptured as the bowel was being dissected out. Death appeared to have been brought about by inanition and terminal multiple pulmonary emboli.

In the large intestine, two types of lesions may be seen — an annular constriction and a destruction of the mucosal pattern with hypermotility and increased irritability.

C. L. (BCH 490440), a 50-year-old woman, was admitted to the hospital on December 27, 1924. A year before she had noted some loss of weight, and on two occasions had passed a small amount of bright blood by rectum. Two months prior to entry she noticed increasingly severe constipation, alternating with short bouts of diarrhea. Six weeks later, there developed a severe dull pain in the right lower quadrant of the abdomen, made worse by eating, and on three occasions during the next month she again passed blood by rectum. Physical examination revealed only a firm, irregular, slightly tender mass the size of a small orange in the right lower quadrant. X-ray examination showed some mottling of the cecum near the ileocecal valve, and the cecum was displaced upward, as if by a mass outside the gastrointestinal tract.

Operation was performed on January 1, 1925, and a large mass was found involving the appendix and the cecum.





FIGURE 5. *Hodgkin's Granuloma before Treatment.*



FIGURE 6. *The Same after Treatment.*

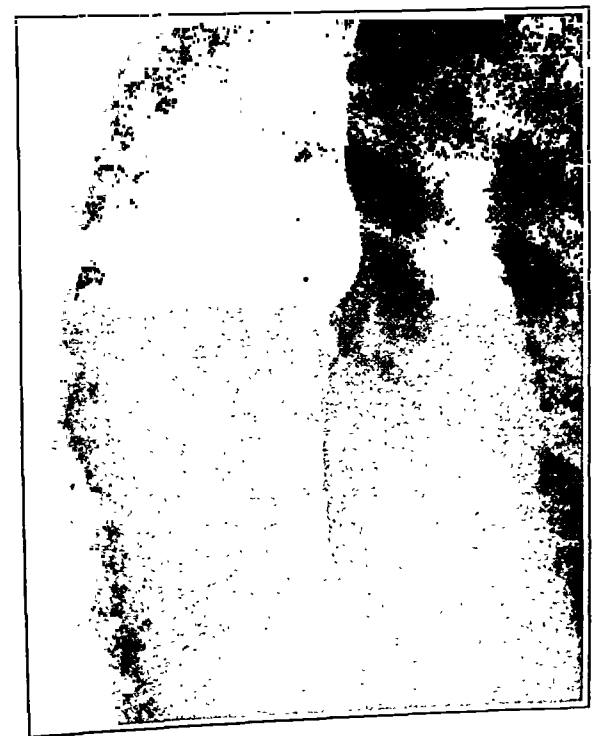


FIGURE 7. *Hodgkin's Granuloma of the Esophagus.*

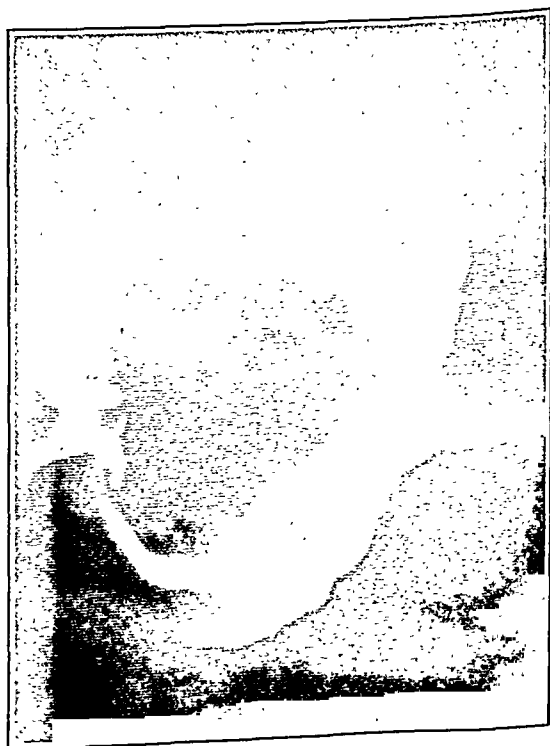


FIGURE 8. *Hodgkin's Sarcoma of the Stomach.*

Only from a series of cases that has been carefully studied and painstakingly followed can one properly judge of the frequency of such changes. We have derived our figures from the cases observed and followed at the Collis P. Huntington Memorial Hospital and the Pondville Hospital. In neither institution have routine bone plates been taken, but each patient has been so studied clinically and radiographically that at least the majority of gross lesions have been detected during life.

One hundred and thirty-three cases of proved Hodgkin's granuloma have been followed to date or to death at these two hospitals only, and of these, 30 (23 per cent) showed during life one or more bone lesions. Both Uehlinger<sup>10</sup> and Dresser<sup>11</sup> found the changes most frequent in the spine and pelvis. Such has also been our experience (Table 5). Dres-

TABLE 5. *Distribution of Bone Lesions during Life in 133 Cases of Hodgkin's Granuloma*

BONES INVOLVED	NO OF CASES
Lumbar vertebrae	14
Dorsal vertebrae	8
Cervical vertebrae	1
Pelvis	7
Ribs	5
Sternum	3
Scapula	2
Sacrum	2
Humerus	1
Floor of orbit	1
Fibula	1
Multiple lesions	10

ser's<sup>11</sup> distribution figures on 66 cases are comparable, although it should be borne in mind that, in all probability, not all his patients had Hodgkin's granuloma.

Age does not appear to be a factor, for cases with bone lesions were distributed almost as evenly throughout the decades as the disease itself (Table 6).

Uehlinger<sup>10</sup> believes that bone lesions occur late in the course of the disease. This is not in accord with our experience, for in 30 cases showing bone

TABLE 6. *Age Distribution of Patients with Hodgkin's Granuloma Who Had Bone Lesions.*

AGE	NO OF CASES
0-9	0
10-19	4
20-29	5
30-39	6
40-49	8
50-59	5
60-69	2

involvement the lesion was found in less than one year from onset in 22 per cent, and in only 6 cases had the disease been present for over four years before the bone change was noted. In 5 cases, the bone lesion was the first recognizable indication of the disease or occurred within six months after its onset. Dresser and Spencer<sup>11</sup> arrived at similar conclusions, for they write, "In our series of 66 cases there were 16 in which the bone lesions gave rise to the presenting symptoms; that is, the bones

were involved early in the course of the disease in nearly 25 per cent." Their figure may be a little too high, for there is good evidence that some of the cases they refer to were actually examples of primary reticulum-cell sarcoma of bone, a condition not described or recognized as such at the time they wrote. In view of the fact that primary reticulum-cell sarcoma of bone is probably best treated by amputation and subsequent prophylactic radiation, it is of great importance to maintain a nice distinction between these two conditions.<sup>12</sup>

The following case illustrates the early bone lesions in Hodgkin's granuloma.

M. L. (P-3650), a 44-year-old man, was admitted to the hospital on August 24, 1931. In the previous January he had complained of severe pain in his right hip, especially on walking. The pain steadily increased, and in June he was admitted to another hospital, where it was noted that there was both cervical and inguinal lymphadenopathy. A biopsy was done, and a diagnosis of Hodgkin's granuloma was made. On September 1, x-ray studies showed a greatly increased hilar shadow. Roentgen films revealed a large bony outgrowth from the lateral margin of the right ilium and considerable lacework-like new bone formation about the upper end of the right femur in the intertrochanteric region and the upper end of the shaft. There was also slight thickening of the cortex of the upper end of the left tibia, and the lumbar spine showed a slight but definite increase in the density of the body of the fourth vertebra. These changes were regarded as consistent with Hodgkin's granuloma. The patient failed rapidly and died on January 23, 1932 (Uehlinger's<sup>10</sup> Case 9 presented a similar x-ray appearance.)

In this case it is clear that the bone lesion first attracted the patient's attention to his condition, and it appears from the history that it occurred early in the course of the disease, if, indeed, it was not the initial lesion.

The roentgen-ray picture is in no way characteristic (Figs. 9-12). It generally simulates metastatic carcinoma, but may be confused with Ewing's tumor, osteogenic sarcoma, osteomyelitis or multiple myeloma. The lesion is usually destructive, especially in the spine, where it occasionally results in the collapse of one or more vertebrae. As a result of this collapse there may be flaccid, or more rarely spastic, paralysis. Paralysis occurred in 8 of our cases in which the spine was involved. It must be remembered, however, that collapse may occur without paralysis, and indeed without symptoms, and, on the other hand, that the vertebrae may be involved by direct extension from adjacent lymph nodes and that simultaneous extension from these same lymph nodes to the dura or the epidural space with tumor formation is probably a much more frequent cause of neurologic symptoms than is vertebral collapse as such. This has at least been our experience.

It is chiefly the bodies of the vertebrae that are involved. More rarely, the transverse processes or the spines are the site of disease. The intervertebral disks are characteristically spared. Occasionally the lesion is chiefly proliferative. Exceptionally one sees the *Elfenbeinwirbel* or ivory vertebrae so

There were several soft lymph nodes in the adjacent mesentery. The mass and the nodes were removed, and an ileocolostomy was performed. On histologic examination the lesion proved to be Hodgkin's granuloma. At operation there was no evidence of disease elsewhere.

The patient died of bronchopneumonia 2 days later. Since there was no autopsy, it cannot be said with any certainty that the disease was confined to the cecum and adjacent nodes, although this seems probable.

In patients with gastrointestinal lesions, an anemia of moderate or severe grade is frequent. We cannot agree that any diagnostic significance can be ascribed to the white-cell count, for both leukopenia and leukocytosis are encountered with equal frequency and indeed often alternate in the same patient. Fever is frequent and was present in 4 of the 6 cases with primary disease in the gastrointestinal tract; in 1 of these it was a striking feature. Since fever is usually present in patients with Hodgkin's granuloma, no special diagnostic importance can be attached to it.

It is doubtful whether a clinical diagnosis of Hodgkin's granuloma of the gastrointestinal tract can be made with any degree of assurance, although the presence of a lesion reminiscent of carcinoma in a patient with an unexplained septic temperature and either a leukopenia or a marked polymorphonuclear leukocytosis not readily explainable on other grounds is suggestive.

*Hodgkin's Sarcoma*

The symptoms referable to the gastrointestinal tract, particularly anorexia, which is often severe, occur in approximately 50 per cent of cases during life (Table 4). Constipation is not infrequent;

TABLE 4. *Gastrointestinal Symptoms in Thirty-Two Cases of Hodgkin's Sarcoma.*

SYMPTOM	NO. OF CASES
Anorexia	14
Constipation	7
Vomiting	7
Nausea	6
Hematemesis	3
Diarrhea	1

diarrhea is rare. Hematemesis, not always explainable either clinically or at autopsy, occurs occasionally. As in the case of Hodgkin's granuloma, gastrointestinal symptoms may occur without any lesion's being demonstrable. On the other hand, it is extremely unusual to have an asymptomatic lesion of the stomach or intestine, such as one not infrequently seen in Hodgkin's granuloma.

Both clinical and autopsy findings indicate that multiple involvement of the gastrointestinal tract is not infrequent. Thus, in 6 cases with clinical evidence of gastrointestinal disease, the colon was involved in 4, the duodenum in 3, the stomach in 2, and the rectum in 1, there being multiple involvement in 3. Again, there is marked contrast to the situation in Hodgkin's granuloma, in which gastrointestinal lesions are almost invariably single.

The following case illustrates the course of Hodgkin's sarcoma when the gastrointestinal tract is involved.

J. C. (BCH 974896), a 52-year-old woman, was admitted to the hospital on March 10, 1940, with the chief complaint of a painless lump in the neck of 2 months' duration. In addition, she had experienced some difficulty in swallowing and hoarseness. She was constantly nauseated and had no appetite, but there was no vomiting. There was marked weakness. She had occasional distress in the left upper quadrant of the abdomen but no real pain. The past and family histories were uneventful.

Physical examination showed a moderately obese woman with a rather sallow complexion. There was a moderately firm mass about 2 cm. in diameter in the right side of the neck. Otherwise the examination showed no notable abnormalities.

X-ray studies of the gastrointestinal tract showed a large, fungating tumor arising from the superolateral wall of the cardia (Fig. 8). Gastric analysis showed normal amounts of hydrochloric acid and a + guaiac reaction. There was no anemia. The white-cell count and differential count were essentially normal. All stools gave a +++ guaiac reaction.

The patient failed rapidly and died on April 20, less than 4 months after the initial symptoms.

*Autopsy.* This showed Hodgkin's sarcoma of the stomach with metastases to the pleura, diaphragm, spleen, liver, large intestine, pancreas and abdominal lymph nodes.

BONES

*Hodgkin's Paragranuloma*

Involvement of the bones does not occur in Hodgkin's paragranuloma.

*Hodgkin's Granuloma*

Lesions of the bones in Hodgkin's granuloma are frequent, important and usually serious.<sup>10</sup> It should be emphasized that we are concerned only with the lesions giving rise to signs or symptoms during life and usually, although not invariably, recognizable by proper radiographic technic. The frequency or paucity of such lesions in no way reflects the incidence of involvement of bones as determined by complete study of autopsy material, for it has repeatedly been shown that medullary lesions demonstrated post mortem may not be detected by x-ray. This fact does not detract from the usefulness of searching for lesions during life.

The frequency of bone involvement at autopsy has already been discussed. Uehlinger,<sup>10</sup> dealing almost entirely with autopsy material, places the incidence as high as 34 per cent, and he expressly states that he is concerned only with Hodgkin's granuloma. Dresser and Spencer<sup>11</sup> say, "One may expect to find roentgen changes ante mortem in approximately 10 per cent of all cases of Hodgkin's disease." The series from which they derived their data, however, included not only that condition but also lymphosarcoma and reticulum-cell sarcoma. Since in our experience bone lesions in the latter conditions are comparatively infrequent, it is probable that the incidence in these authors' series of Hodgkin's granuloma was, in actuality, higher than that reported.

accurately described and superbly pictured by Hultén.<sup>13</sup> Not infrequently both new-bone formation and bone destruction are present. Very rarely multiple punched-out areas indistinguishable from those of multiple myeloma are seen.

Pathologic fracture occurs rarely. We have seen only one example, and that in a rib. In contrast, pathologic fracture is fairly frequent in primary reticulum-cell sarcoma of bone.

Periosteal new bone formation may be seen alone or, oftener, in conjunction with medullary lesions.

In the long bones the metaphyses are chiefly involved. Dresser and Spencer<sup>11</sup> report involvement of the shaft. This we have not seen.

The ribs, especially those portions close to the vertebrae and sternum, are frequent sites of invasion. The sternum may be invaded directly from an underlying mediastinal mass, and it is of some practical importance that such sternal lesions seem to do exceptionally well under treatment. The pelvis is oftenest involved in the region of the iliac crest or the sacroiliac joints.

Unequivocal cases of Hodgkin's granuloma confined to bone have not been described.

Uehlinger<sup>10</sup> and others believe that abnormalities of the peripheral blood picture, especially leukopenia, are frequently the best indication of a bone lesion. We have not found this to be so. Neither the red-cell nor the white-cell count altered in any material manner after the development of the bone lesion. Of the 2 cases with the most extensive bone changes in this series, one showed a marked polymorphonuclear leukocytosis, and the other a moderate leukopenia. Both had only a moderate degree of anemia, even at the time of death. We have seen no evidence that an eosinophilia is indicative of bone involvement as some have claimed.

The most frequent symptom is pain, and when one considers that the patient's attention may be drawn to his condition primarily by the bone lesion and that lymphadenopathy may be minimal at that time, and therefore often overlooked, the importance of the search for and recognition of early bone lesions is obvious.

It is important further to recognize that pain due to bone lesions may be present for a considerable period of time before the x-ray films show any recognizable change. In 13 per cent of our cases with bone lesions, pain was present for a period of two to twelve months before the lesion was visualized, in spite of repeated x-ray examinations. The therapeutic implications of this observation are obvious. In the presence of proved Hodgkin's granuloma, the appearance of pain referable to a bony structure or a joint may properly be regarded as an indication for irradiation even though no bony lesion can be found at the time. On the other hand, one occasionally finds on routine x-ray examination gross bone lesions without concomitant symptoms. This is particularly true of the skull,

invasion of which frequently gives no other clinical evidence than the appearance of a soft-tissue mass directly over the area of bone destruction. Similarly, lesions of the pelvis are apt to be painless unless they involve the sacroiliac joint or the hip joint. Under the latter circumstances, the pain is apt to radiate down one or both legs and be mistaken by the unwary for back strain or simple "sciatica." Tenderness over involved bones is surprisingly infrequent.

#### *Hodgkin's Sarcoma*

Clinically apparent involvement of bone is comparatively infrequent in Hodgkin's sarcoma, occurring in less than 10 per cent of our cases. In one case, there was a small destructive lesion in the upper end of one tibia. In another, there was a localized, proliferative lesion in the upper end of the femur. In still another, there was an extensive destructive process of the skull. In a fourth case, there was direct extension from the pharynx into the bony structure of the antrum, causing severe and intractable pain. In all the other cases, the bone lesion resulted merely in a moderate degree of pain.

In our experience, the bone lesions usually occur early in the course of Hodgkin's sarcoma. They may appear later, but in view of the fact that the majority of patients die within a year and a half of apparent onset, such observations on the time of appearance of the bone lesions are of little practical value.

#### SKIN

##### *Hodgkin's Paragranuloma*

Skin lesions do not occur in Hodgkin's paragranuloma.

##### *Hodgkin's Granuloma*

Skin lesions in Hodgkin's granuloma are of common occurrence.<sup>14, 15</sup> Severe generalized pruritus, not infrequently resulting in marked excoriation of the skin, is perhaps the most frequent one. Generalized or, more rarely, localized pigmentation occurs aside from that due to radiation therapy. Herpes zoster (Fig. 13), not infrequently of a hemorrhagic type and often leaving behind it an indurated scar (Fig. 14), is not unusual. The more specific lesions, — that is, those which on biopsy show the characteristic features of Hodgkin's granuloma, — are most frequently nodular (Fig. 15) or ulcerated (Fig. 16). These may exist for a long time prior to unequivocal evidence of the disease elsewhere.<sup>16</sup> Generalized exfoliative dermatitis has been reported, and we have seen 1 case with this complication.

##### *Hodgkin's Sarcoma*

In Hodgkin's sarcoma, lesions of the skin occur in approximately 30 per cent of the cases and may



FIGURE 9 *Proliferative Lesion of the Femur*



FIGURE 10 *Destructive Lesion of the Ilium*

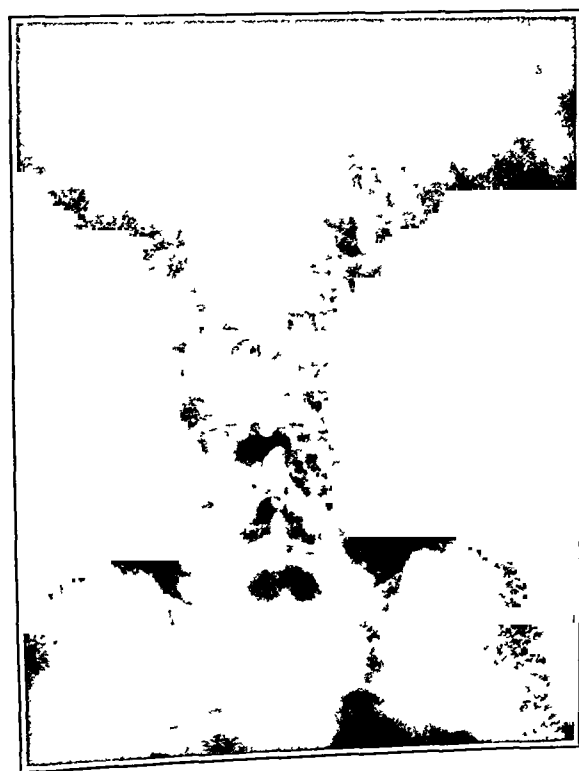


FIGURE 11 *Proliferative and Destructive Lesions of the Spine*



FIGURE 12 *Hodgkin's Sarcoma of the Skull*

be extremely marked. They are usually papular, and dull red and frequently scaly, resembling closely the lesions of mycosis fungoides. Rarely there are subcutaneous lesions 1 to 3 cm. in diameter. We have never seen ulceration.

Patchy or extensive erythematous lesions are occasionally seen. Itching is extremely rare.

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## THE INCREASING COST OF MEDICAL CARE: ITS RELATION TO HOSPITALS AND SPECIALIZATION IN MEDICINE\*

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THE purpose of this paper is to state briefly the causes that, in my opinion, have led to an increase in the cost of sickness, to review the various attempts that have been made to meet it, and to suggest certain lines of approach that might lead to a solution of the problem.

The present high cost of sickness had its beginning in the latter part of the last century, and is due almost entirely to the rapid advances of medical science and the general acceptance of the community hospital instead of the home as the best place for the care of the sick. That both these trends are sound is shown by the rapid growth of specialization in medicine and the increasing use of hospital service by the well-to-do, the patient of moderate means and the practitioner of medicine.

Fifty years ago the care of sickness in those able to pay was largely in the hands of the family physician. The indigent were cared for in the great charity hospitals. There were very few so-called "private hospitals." Even such major therapeutic procedures as surgical operations were often done in the home. When the cause of the illness could not be established, or the patient did not improve under treatment, a consultation was sought. Often another general practitioner was called; at times, the advice of a surgeon or some other specialist was obtained. In either case, the patient remained in his home and was cared for by the members of the household. Only the well-to-do employed a professional nurse.

An accident that occurred in my own family some fifty years ago will serve as an example to

contrast the procedure then and now. My brother, a boy of ten, fell from a scaffold in the barn, fracturing his femur in the middle third of the bone. Our family doctor was called, the diagnosis was established, a temporary splint was applied, and the patient was placed in his bed. Of course there was no x-ray examination, and I doubt very much if any search was made for injury elsewhere in the body. In due time the doctor returned with some cords and pulleys, which he had obtained from the hardware store, a can of ether and some adhesive. My father gave the ether under the doctor's direction. The fracture was reduced, and the splints and traction were applied. My mother and other members of the family attended to the nursing care. The fracture healed in the usual time; there was no deformity or limp. The doctor's bill was twenty-five dollars, and there were no other expenses.

Now, let us consider what would happen if the same accident occurred today. My father was a prosperous farmer and would have been classified in the "moderate means" group. The boy would have been taken to the hospital, roentgenograms would have been taken before and after reduction, and the operation would have been done by a surgeon who would have required two assistants, with the usual nurses. There would have been an operating-room charge, the routine laboratory charges and the charges for room, board and nursing care during the stay in the hospital. This would have constituted the hospital bill and would have had to be paid at once. In addition, there would have been the surgeon's fee and the x-ray charges. A moderate estimate of the total cost would be between five and six hundred dollars, which is more than the

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FIGURE 13. *Hemorrhagic Herpes.*



FIGURE 14. *Scar following Herpes.*



FIGURE 15. *Nodular Lesions.*



FIGURE 16. *Ulcerative Lesions.*

placed on a full-time salaried basis. This was also a departure from established custom in hospital-staff relations. Since the simple plan, worked out at that time, has been in operation for twenty-eight years with complete satisfaction to all concerned, it would seem that it might be considered as a basis for the establishment of hospital-staff relations in other branches of medicine and in other hospitals. The following abstract presents the important features of this plan.

The roentgenologist is to give his entire time to the work and the direction of the work done in the roentgenologic department of this hospital, excepting such teaching as may be required of him by the Harvard Medical School and its postgraduate school. The amount of this teaching is controlled by the executive staff of the hospital and the faculty of the school. According to this arrangement the roentgenologist is to receive a yearly salary of a stated amount, but should the income to the hospital from his work in connection with the private pavilion at any time considerably exceed the expense of maintaining this branch of the work plus his salary, he is to receive a proportionate part of such earnings. It is also understood that the roentgenologist may reduce his earnings from private fees if he so desires in order that he may have sufficient time for research.

In other words, the roentgenologist is allowed to control his income and the character of his work within reasonable limits. The general principles of this plan can be applied to any form of hospital-physician arrangement.

If a working agreement of this sort could be established between the hospitals and their medical staffs, the only problem remaining would be that of arranging the cost to the individual patient in such a way that it could be met without too much difficulty.

The cost of hospital service is already being handled satisfactorily by such forms of voluntary insurance as the Blue Cross. This type of insurance is inexpensive, and it protects the patient against the largest and most urgent expense in case of illness. It should be encouraged and expanded.

As yet no satisfactory form of insurance against the cost of medical service has been devised, although many attempts to do so have been made, and the literature on the subject is voluminous. Faxon,<sup>1</sup> in a recent paper, has discussed the advantages and disadvantages of voluntary and compulsory insurance. A symposium on this subject was conducted at the annual meeting of the American Medical Association in June, 1944. Of the various plans discussed at this symposium, that presented by McCann<sup>2</sup> seems the most likely to be workable, and it is the plan sponsored by the Massachusetts Medical Society.

One of the stumbling blocks in all the plans suggested has been the high cost — to the patient, to

the state or to the medical profession. Any plan to cover the complete cost of sickness must of necessity be expensive and will not be voluntarily accepted by the public. One reason why complete health insurance is expensive is because it tends to increase the number of patients applying for treatment. It is a well-known trait of human nature to feel dissatisfied when there is no return from an investment in protection, and as a rule an attempt is made to get something back, especially if this can be done without additional cost. Insurance companies have long recognized this fact, and have met the problem by providing cash returns at a specified time, or by requiring the insured to pay a part of the initial cost.

If an insurance plan to protect the paying patient against the cost of specialized medical service could be worked out, it might offer a satisfactory solution of the problem. By "specialized medical service" is meant all consultations and such therapeutic procedures as require special training on the part of the physician. It does not mean routine visits and treatment by the attending physician. Such a plan would not disturb the present relation between the patient and the family physician. It would operate only when the patient's illness was such that hospitalization and the advice of, or treatment by, a specialist became necessary. If the amount allowed for any one illness were limited, it would tend in the long run to establish a standard of charges for specialized services, and since the patient would have to meet the first cost, — that of the family physician, — it would not be abused. The amount necessary for such coverage would therefore be low enough to make it attractive and to ensure its general acceptance. There are, of course, many difficulties to overcome, most important of which is a satisfactory arrangement between those doing specialized medicine outside the hospital and those doing all, or the greater part of, their work within the hospital. None of these difficulties, however, are insurmountable, and all could, I think, be solved by a properly selected board. It is possible that the Blue Shield, sponsored by the Massachusetts Medical Society, could be modified to meet the requirements.

\* \* \*

In conclusion, the following statements seem to summarize the problem.

There is widespread demand on the part of the public for a plan to meet the increasing cost of sickness. This problem should be solved by the medical profession, not by the state.

The increase in the cost of sickness is largely due to the increasing demand for hospital care and specialized medical service.

There must be a clear understanding of what constitutes hospital service and of what constitutes



average farmer can meet without considerable sacrifice. Is it any wonder that there is a widespread demand on the part of the public that some plan be devised to safeguard it against the high cost of sickness?

The answer is not in a return to old methods. In the case just described, the boy was fortunate that the fracture did not involve the epiphyseal line and that no internal injury occurred. Under the treatment that he received the former would have resulted in a short leg, the latter possibly in his death. Present-day treatment would meet successfully both these problems.

Nor is it possible to care for the sick in the modern home. Space is limited, domestic help, which used to be the rule, is now the exception, and modern diagnosis and treatment require elaborate equipment, all of which is available in a hospital.

The services of the family doctor may still be had at only a slight increase in cost. Probably the average family today pays no more to the family doctor than did their fathers before them. The increased cost, of which one hears so much, is then almost entirely due to hospital service and the fees of the specialist. If these were taken care of, the well-to-do and those of moderate means would be able to receive the benefits of modern medicine, already supplied free to the poor, without having to meet any greater financial burden than they have been able to carry in the past. If this general statement of the problem can be accepted, the solution seems to lie in the providing of some form of insurance, first against the cost of hospital care, and second against the cost of specialized medical care.

Before attempting to set up any form of insurance against the cost of sickness it is necessary to have a clear understanding of what constitutes hospital service and what constitutes medical service. The first objective of a hospital is to furnish housing and nursing care for the sick; its second is to provide the laboratories and tools with which the physician makes the diagnosis and carries out treatment of the patient. Together the medical staff and the hospital should form a center for the advancement of medical knowledge and the improvement of the general health of the community. The early hospitals were charitable institutions supported either by donations or taxation. They were expected to operate at a loss. They received no private patients, and medical service was free. In other words, the community supplied the funds for the maintenance of the hospital, and the members of the medical staff donated their services. The problem of what constituted medical or hospital service did not arise. It was only with the introduction of the paying patient into this established setup that a definition became necessary. It is probably fundamentally wrong to pay for medical service out of funds raised for the maintenance of the hospital, or to use a

part of the medical fee for hospital support. Both tend to lower the standard of medical service, and in the long run the patient is the loser. In the care of the paying patient, the hospital, as in any other business venture, is entitled to a reasonable profit on its investment. The doctor, on the other hand, should charge only what he considers a fair return for his services. He should not divide his fee with a third party even if the third party is a charitable institution.

It is recognized that for the hospital to carry out its function, certain members of its staff must spend a part, or the whole, of their time in administrative work. The salaries that these men receive for this type of service are part of the cost of maintaining good hospital service, and should be considered as part of the cost of hospital care in those hospitals that receive paying patients, as well as in those in which the general medical service is free. It has become a custom for members of the medical staff to spend a considerable part of their time in the diagnosis and treatment of paying patients within the hospital. This is desirable from the point of view both of the doctor and of the hospital. The increased income that the doctor receives in this way tends to raise the standard of services both to the hospital and to the patient. It makes no real difference whether the medical fees are collected by the hospital and returned to the doctor in the form of a salary or whether he collects his own fee, provided that the hospital recognizes the principle that it is not to make a profit from the collection of medical fees.

If the income from medical fees is divided between the physician and the hospital, the cost to the patient for that particular service is increased by whatever profit the hospital makes from such practice. In other words, the hospital is forcing each paying patient to make a contribution toward the support of some other department of the hospital. This practice is not only unfair to the paying patient but also tends to disturb interdepartmental relations of the hospital. The department showing a substantial profit is apt to be given undue importance in general planning. Any increase in hospital charges, beyond that which is based on hospital service, is in the long run injurious to the patient, the hospital and the physician.

One has a right to assume, I think, that both the hospital and the members of its staff are anxious to have their patients receive the best possible service at a minimum cost consistent with that service. Any plan that tends to defeat this object should therefore be avoided.

In 1916, the Massachusetts General Hospital, in response to popular demand, opened a pavilion for the care of private patients. This was a radical departure from a long-established practice. At the same time it arranged for its roentgenologist to be

that I have never seen a case in which a portion of the stomach was removed for carcinoma and the patient had a recurrence after remaining free of one for thirty-five years, so I do not anticipate any recurrence in this case. I think that we are both fortunate to be here before this society.

319 Longwood Avenue

### DISCUSSION

DR. PHILEMON E. TRUESDALE, Fall River: Any good news on the surgical treatment of cancer of the stomach is welcome. Dr. Lund has created what seems to me to be a record title for himself and his patient. In addition to that, he has cast a bright spot on an otherwise extremely drab picture — that of the surgical treatment of cancer of the stomach, the location where one third of the cancers of the body occur.

In making a study of our cases of cancer of the stomach, I find that we have treated 85 cases surgically. Gastroenter-

and causes obstruction early there is generally an opportunity for radical operation. If it is discovered by palpation, as with a tumor invading the greater curvature of the stomach, the case may be hopeful, but one never knows what patient is operable and what patient is inoperable until he opens the abdomen. Until there is some other more effective means for the early detection of cancer of the stomach, we must rely on exploratory laparotomy to differentiate the operable and the inoperable cases.

DR. DAVID CHEEVER, Boston: Was there a pathological note on the condition of the lymph nodes?

DR. ARTHUR W. ALLEN, Boston: I did not expect to discuss Dr. Lund's paper, but I am so delighted that he can report such a remarkable cure of carcinoma of the stomach, that I should like to make a few remarks on this subject.

In a group of patients followed by Parsons at the Massachusetts General Hospital the end results about ten years ago showed a five-year curability rate of about 20 per cent. This included the operative mortality, which was about 35 per cent. Five years later Parsons and Welch reported an-



FIGURE 1.

ostomy was done in 38 of these. This operation has been abandoned for the last decade. Forty patients were treated by gastric resection, and 7 patients had a total gastrectomy. The mortality of gastroenterostomy was 26 per cent and that of partial gastrectomy 22 per cent. In 7 cases of total gastrectomy, the mortality was 29 per cent.

It is needless to say anything about the results of gastroenterostomy. They were invariably unsatisfactory. But of the patients who had a partial gastrectomy, 1 lived for sixteen years and died of arteriosclerosis, 3 lived for ten years, 3 lived for five years and 2 lived for four years.

Of the patients with total gastrectomies, 2 died in the hospital, 3 died within a year, 1 is living two years after operation, and 1 is living three years after operation.

It seems to me that we can gather a little comfort from this, but the case that Dr. Lund has told us about eclipses my report of results after surgical treatment of cancer of the stomach.

The diagnosis of cancer of the stomach is not easy. The patient seldom comes to the physician until the disease is advanced. If the disease happens to be near the pylorus,

other series of cases. The resectability had increased about 10 per cent. and the operative mortality rate had decreased about 10 per cent. In spite of this, there was only an additional 1 per cent added to the number of five-year cures. In other words, as the development of more radical surgery came along, the actual number of five-year respites had not appreciably increased. There were, however, a great many additional added months of life and comfort for this group of patients.

So often we have had the experience of doing a long, hard resection, taking all the strength that one has to put into any effort in one day, only to have the patient live a short period of time. This, of course, is terribly discouraging. On the other hand, we have had many patients with extremely malignant carcinomas of the stomach, including positive lymph nodes, live for several years after resection.

The first total gastrectomy that I did was in an extremely unfavorable case — Grade 4, with positive nodes. The patient lived for four years and eight months and worked four years of that time. He finally died of recurrence.

The question whether these patients are operable can often

medical service. Neither the hospital nor the physician should receive financial returns for services rendered to the patient by the other.

Plans such as that of the Blue Cross to cover hospital service should be encouraged and expanded.

A plan of insurance to cover the cost of specialized medical service should be developed.

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## PARTIAL GASTRECTOMY FOR CARCINOMA THIRTY-FIVE YEARS AGO\*

FRED B. LUND, M.D.†

BOSTON

SOME of you may have noticed that there is a war in progress, as a result of which we are restricted in gasoline. Therefore, in order to go to Boston last winter, I embarked on the Worcester bus. A Joseph Dawson, who was a fellow passenger and whom I have asked to appear before you today, recognized me and asked me whether I remembered him. I had to confess I did not, when he told me that I had operated on him for removal of carcinoma of the stomach thirty-five years before. I then remembered him very well, because I had followed his case for about twenty years before losing track of him.

This patient was admitted to the Boston City Hospital on August 16, 1909. He was forty-four years old, born in England. Four or five years previously he had been laid up for a couple of weeks with gallstones but was not operated on. He had severe pains in the right side. Two or three years previously he had "neuralgia" around the heart, and he had also had "malaria" off and on for seven years. Since early spring he had had continuous dull pain in the region of the stomach two or three hours after eating, and then vomited dark, almost black vomitus, especially after eating fruit. He had done this two or three times a week for two or three months. His weight had dropped from one hundred and fifty-eight pounds to one hundred and thirty pounds, and he was sallow and cachectic-looking. The skin was yellow, but the scleras were white and clear. He was somewhat emaciated. There was tenderness over the epigastrium and in the midline. Five centimeters above the umbilicus was a movable tumor, hard, round and about the size of a tennis ball.

At that time x-rays were not available for the study of such cases. Examination of the stomach contents showed no stasis, no lactic acid and no free hydrochloric acid. The guaiac test was positive for blood. The hemoglobin was 80 per cent, and the differential count showed 70 per cent polymor-

phonuclear cells and 23 per cent lymphocytes; there was slight achromia.

On August 17, the abdomen was opened under ether anesthesia and a large mass was found on the greater curvature of the stomach, extending from the anterior surface around to the posterior surface above the pylorus. The stomach at the site of the mass was slightly adherent posteriorly. The gastrocolic omentum contained firm, hard lymph nodes. The nodes were freed from the omentum, and the stomach was clamped off just to the right of the pylorus and at about its middle above the mass. About half the stomach was removed between the clamps, together with the lymph nodes. The open end of the stomach was closed with layer sutures, and the duodenum with a double purse-string suture. A posterior gastroenterostomy was then done, close to the beginning of the jejunum. The mesocolon was sewed to the stomach, and the wound closed in layers. This type of operation was then known as the Billroth No. 2.

The patient vomited once the following morning. The temperature on the first day after operation went as high as 98.6°F. Afterward it ran on a normal line. Feeding was begun at once and was rapidly increased. The stitches were removed on August 24, and the patient left the hospital on August 31. The pathological report was as follows:

There is a tumor that has replaced the mucosa in one area and has extended downward through the muscularis mucosae. The tumor is composed of large cells, with big, often irregular, nuclei. Mitotic figures are numerous. The tumor is growing as groups and masses of cells, with occasional lumen formation. There is an extensive infiltration of lymphocytes, some plasma cells and a few polymorphonuclear leukocytes around the neoplastic cells. Microscopic diagnosis: Poorly differentiated, rapidly growing carcinoma.

The original section (Fig. 1) has been reviewed and there appears to be no doubt concerning the accuracy of the diagnosis.

Ever since the patient was operated on he has been in good health and hard at work as a machinist. At the time of the operation, he was forty-four years old, and so was I. I can tell him truthfully

\*Presented at the annual meeting of the New England Surgical Society, Boston, September 20, 1944

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## MEDICAL PROGRESS

### ENDOSCOPY\*

EDWARD B. BENEDICT, M.D.†

BOSTON

THE recent advances in endoscopy may be reviewed under a variety of headings.

#### ANESTHESIA

Whalen<sup>1</sup> has reviewed the various sedatives and anesthetics that are useful in peroral endoscopy. In adults he advises 0.1 gm. of Nembutal at bedtime and again about half an hour before the operation. He also advises 16 mg. of morphine and 0.6 mg. of scopolamine. In children, an open capsule of Seconal Sodium placed in the rectum one hour before the examination is often sufficient to render the patient quiet and controllable. The toxic reactions from cocaine are counteracted by the use of one of the barbiturates for preanesthetic medication; 5 per cent cocaine is recommended. If general anesthesia is required, intravenous Pentothal Sodium is satisfactory. In cases in which there is spasm of the cricopharyngeus muscle, entrance to the esophagus has been easy after the use of curare, which is now on the market under the name Intocostin. Avertin is used infrequently because of the respiratory depression, the slow return of reflexes and the frequent necessity of supplementing anesthesia. Toxic effects from scopolamine may be counteracted by the use of 1.5 mg. of apomorphine.

#### BRONCHOSCOPY

##### *Bronchitis*

Holinger and Rigby<sup>2</sup> report 69 patients with fusospirochetal tracheobronchitis. Infections due to these organisms are usually associated with copious, foul expectoration, lung destruction and abscess formation or extensive bronchiectasis. The clinical features of fusospirochetal tracheobronchitis resemble those of pulmonary tuberculosis, including cough, loss of weight, fatigue, occasional hemoptysis and night sweats. The bronchoscopic findings consist simply of chronic bronchitis. The mucosa is injected, and a small amount of mucopurulent secretion may be present. The principal therapeutic agents are the arsenicals or autogenous vaccines, which may be employed, and bronchoscopic aspiration is used to relieve bronchial obstruction.

##### *Bronchiectasis*

In a study of the etiology of bronchiectasis, Olsen<sup>3</sup> studied 85 patients who had congenital dextro-

cardia. Fourteen of these patients also had bronchiectasis. The frequency with which bronchiectasis accompanies visceral transportation lends support to the theory of the congenital origin of many cases of the disease. A consideration of the evidence in favor of both theories of the origin of bronchiectasis — viewed as congenital and as acquired — indicates that both congenital and acquired components enter into the production of most cases of the disease.

Rilance and Gerstl<sup>4</sup> have reported a series of tuberculous patients in whom bronchiectasis assumed a place of major importance in the evolution of the pulmonary lesion and the development of the terminal pathologic condition. Bronchiectasis secondary to tuberculosis has repeatedly been demonstrated in tuberculous patients. Few of these patients, however, exhibit any significant symptoms due to the complication, and it seems likely that in the majority of them bronchiectasis is merely a benign bronchial dilatation not associated with abnormality of bronchial function. A minority appear to develop a true suppurative bronchiectasis that many times, both in severity of symptoms and in the resultant disability, overshadows the tuberculous parenchymal disease. It seems justifiable to assume a different etiologic basis for the two types of bronchiectasis. A series of 47 patients with significant degrees of bronchiectasis in association with tuberculosis was studied. Twelve patients came to autopsy; 35 were studied by bronchography. The clinical picture and the appearance of the x-ray films of these patients demonstrated the marked similarity that sometimes exists between the manifestations of tuberculous bronchiectasis and those due to active pulmonary tuberculosis. These authors believe that the symptoms of suppurative bronchiectasis secondary to pulmonary tuberculosis may so closely simulate those of active tuberculosis that errors in differentiation may readily be made. Occasional patients, not cognizant that they have had tuberculosis in the past, present themselves for the first time with symptoms due to a suppurative bronchiectasis that may readily be mistaken for active pulmonary tuberculosis. Suspicion of the presence of tuberculous bronchiectasis should be aroused when patients show the clinical symptoms usually interpreted as evidence of active tuberculosis, in association with either a persistently negative sputum or an x-ray picture that by itself would be interpreted as a healed tuberculous lesion. When all three conditions prevail, the evidence suggesting bronchiectasis is extremely strong. The authors

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be settled by peritoneoscopy. This procedure is a real contribution. If Dr. Benedict or Dr. Wallace finds by peritoneoscopy that the liver or peritoneum is involved, we may save that particular patient a needless exploration. In Parsons's first group of patients, exploratory laparotomy alone in the inoperable group gave an operative mortality of 25 per cent, so that this procedure is not so innocuous as one might think, whereas peritoneoscopy carries an extremely low mortality. Of the first group of 20 cases that Dr. Benedict peritoneoscoped, and in which he saw no reason why the lesions should not be removed, eighteen of the latter proved to be resectable. Only adherence to the pancreas is not made obvious by this particular procedure.

The last point that I should like to make is the question of the differential diagnosis of ulcer and cancer of the stomach. It was of considerable importance to us to find that on analyzing a ten-year group of patients with a diagnosis of ulcer of the stomach in our hospital, 14 per cent of them finally proved to have cancer. Patients with apparently benign lesions from a clinical standpoint, with high gastric acidity and typical ulcer pain, were symptomatically relieved on an ulcer regimen in the hospital and finally proved to have cancer. Frequently enough the roentgenologist would say that the ulcer was healing, or was no longer present, after a month's treatment, and on occasion the gastroscopist would find that he could no longer see the crater of the ulcer — only to have such a patient return in three to twelve months with an inoperable cancer of the stomach.

It certainly is worthy of consideration on the basis of this experience to revise our previous ideas concerning gastric ulcer. We should not consider gastric ulcer and duodenal ulcer in the same light. We have not studied our patients sufficiently to say whether the gastroenterologists can relieve as high a percentage of benign gastric ulcer by their conservative methods as they can of duodenal ulcer. Other reports from other clinics, however, stated definitely that the conservative method of treatment of gastric ulcer is unsatisfactory in at least 50 per cent of the patients. This is certainly 30 per cent less than the satisfactory results obtained by conservative methods of treatment of duodenal ulcer. When one adds this factor to the fact that gastrectomy for gastric

ulcer is infinitely a safer procedure than gastrectomy for duodenal ulcer, because in gastric ulcer the duodenum is normal and the treatment of the duodenal stump presents no hazard, — together with the difficulty in ruling out cancer, — it seems to me that we should be more radical in our attitude about gastric ulcer. My conception is that we should consider gastric ulcer fundamentally a surgical lesion, and duodenal ulcer primarily a medical lesion.

DR. CHARLES L. LARKIN, Waterbury, Connecticut: I do not wish to detract from Dr. Lund's operation or his ability to remove cancer of the stomach, but in view of the recent work of Dr. Green, the pathologist at the New Haven Hospital, I raise the question whether there is not a possibility that the tumor that was removed by Dr. Lund was not a cancer of the stomach.

Dr. Green has, as you probably know, been transplanting all suspected cancers that have been removed at his hospital into the anterior chamber of a rabbit's eye. He believes that every real cancer will transplant 100 per cent and that if it is not a cancer it will not transplant. In other words, he thinks that simple microscopical examination is not enough to prove that a cancer is a real cancer. He believes the real test is the biologic test.

It is quite probable that the tumor that Dr. Lund removed would not have proved to be a cancer by the biologic test, although microscopically it is typical.

DR. LUND (closing): There was no note on the lymph nodes. I should like to have had an examination of them.

I am sorry to say that I have not kept a record of all the cancers of the stomach I have operated on. I had one patient who lived for over fifteen years, but in most of my cases there were recurrences in three to five years or even before.

In regard to the tumor's not being a cancer, the patient had the proper chemical content of the stomach and a hard, ulcerated, proliferating tumor, with grossly positive nodes. You saw the section. Dr. Mallory reported carcinoma ventriculi, and Dr. Parker wrote the report that I read to you — so, in my opinion, this was a cancer, and I hope that they won't take it away from me.

faithfulness of the patient in carrying out the prescribed postural drainages, and in part on whether the good effects of aeration and of whatever reduction in infection of the bronchial mucosa occurs as a result of the improved drainage predominate over a recurrence of the mucosal swelling, which presumably may occur as a secondary reaction to the drugs that were used to shrink the mucosa. Experience has shown that, in a few cases, one bronchoscopic treatment removes all the particularly distressing symptoms for an indefinite period of time. In a greater number of cases no relief of symptoms occurs, and in rare cases the symptoms are made worse through an acute attack of pneumonitis. In a majority of patients a satisfactory improvement takes place, but in the course of a week, several weeks or months a relapse occurs, calling for another bronchoscopic treatment. In patients who are indefinitely relieved by one bronchoscopic treatment, or who are not relieved at all, further treatments are obviously not indicated. In the other patients, repeated bronchoscopies are indicated at whatever intervals — five days, several weeks or months — the circumstances require.

#### *Foreign Bodies*

Hartley<sup>8</sup> has discussed a case in which a 10-cm. packing nail remained in the bronchus for thirteen years and was discovered accidentally during a routine x-ray examination of the thorax. For two years after aspirating the nail the patient had no symptoms referable to the chest. Eleven years later, however, he was admitted to the hospital because of fever and pain in the right side of the chest, and x-ray examination showed pneumonitis and pleural effusion, which cleared up spontaneously. The nail was not removed. In contrast to this the author cites the case of a boy four and a half years old who had persistent, violent cough for a two-year period owing to the presence of a wood screw in the left lower lobe of the bronchus. This bears out the well-known dictum that metallic foreign bodies cause much less disturbance than do vegetable ones.

#### *Adenoma*

Lowry and Rigler<sup>9</sup> have reported a clinical and roentgenologic study of 7 cases of adenoma of the bronchus. They note the important fact that there is often extension of the tumor through the bronchial wall, with formation of an extrabronchial mass that may be larger than the intrabronchial portion. They emphasize the fact that although adenoma of the bronchus almost always remains benign so far as lethal metastasis is concerned, its effects on the lung are extremely serious and in many cases ultimately cause death. They also stress the fact that differentiation of benign from malignant tumors of the bronchi is not always possible from the bronchoscopic biopsy material alone. In one of the cases reported the adenoma existed for thirteen and a half

years and terminated with metastases to the opposite lung. In a second case the more usual solid form of the neoplasm was at first mistaken for a so-called "oat-cell carcinoma." The opinion of some investigators that bronchial adenoma is always a benign tumor is rejected. Because of the potentially malignant characteristics, early lobectomy or pneumonectomy is considered the treatment of choice.

Laff and Neuburger<sup>10</sup> also stress the potentially malignant character of neoplasms diagnosed as bronchial adenomas manifested in their invasive growth — extrabronchial extension — and their ability to produce late metastases. Their histologically benign appearance is not incompatible with biologically malignant behavior.

Moersch<sup>11</sup> in discussing the diagnostic abnormalities of bronchiogenic carcinoma refers to adenoma of the bronchus, stating that pathologists differ whether the tumor should be regarded as a benign lesion or as one of a low degree of malignancy. Adenoma of the bronchus has a tendency to recur, and cases have been reported in which the adenoma has infiltrated and involved the mediastinal lymph nodes. At present, Moersch believes that if the tumor is pedunculated and is situated in one of the main stem bronchi, where it can readily be reached through a bronchoscope, it is best treated by bronchoscopic means. All the patients in this category whom he has treated bronchoscopically are still living and well. If, on the other hand, the tumor is situated where it cannot readily be reached bronchoscopically, or if it tends to infiltrate through the wall of a bronchus, or if much secondary pulmonary suppuration is present, Moersch believes that the condition is best handled by surgical means.

#### *Carcinoma*

In a recent article Blake<sup>12</sup> discusses the relation of chronic irritation to carcinoma. In the case reported, a chronic irritating factor — namely, a metal crucifix — was present in the bronchus for a number of years, with subsequent development of primary bronchiogenic carcinoma at the sight of the irritant. The crucifix did not cast a demonstrable shadow in the x-ray film. On bronchoscopy the right middle lobe bronchus was almost completely occluded by a granular mass 1 cm. from the orifice; a preliminary diagnosis of bronchiogenic carcinoma of the right middle lobe bronchus was made. A biopsy was performed, and the tissue removed was considerably larger than anticipated. Pathological examination of the material revealed a crucifix measuring 4 by 7 mm. embedded in the tissue, and a diagnosis of carcinoma was made. Exploratory thoracotomy was done, and revealed an inoperable anaplastic carcinoma of the right middle lobe. The carcinomatous tissue was found to involve the pericardium, the great vessels and mediastinal lymph

point out certain characteristics of tuberculous bronchiectasis that appear to differentiate it from the nontuberculous type.<sup>2</sup> Following the instillation of lipiodol into the bronchial tree, gross distortion and abnormal angulation of the bronchi, changes not usually found in cases of nontuberculous bronchiectasis, were frequently seen. Cystic bronchiectatic cavities, located in the shrunken upper lobe, appeared to simulate in every respect the usual roentgenographic appearance of chronic tuberculous cavities. The assumption that these bronchiectatic cavities were in reality re-epithelialized tuberculous cavities seems to be supported by the pathologic findings reported in one case.

In studying the treatment of bronchiectasis, Stacey<sup>5</sup> reports that sulfathiazole may be applied locally to the tracheobronchial tree by inhalation of nebulized solutions of its sodium salt and that its use in a small series of cases of bronchiectasis has resulted in distinct benefits. The first 3 patients reported were suffering from acute infections, and in these the improvement was rapid and dramatic. No systemic reactions were noted, and no untoward local effects resulted from the treatments.

Oatway<sup>6</sup> reports the use of sulfadiazine, sulfamerazine and sulfathiazole in 48 cases with purulent bronchial secretion. The diagnosis was chronic bronchitis in 11 cases, bronchial asthma with bronchitis in 11, and bronchiectasis in 16. The author is concerned chiefly with the 16 cases of bronchiectasis. The symptoms had persisted for one to twenty-five years. The daily volume of sputum varied between 20 and 800 cc. Administration of sulfonamides by mouth was found regularly effective in all cases of simple, uncomplicated bronchiectasis. The sputum was reduced in all cases, with an average decrease of 62 per cent. In the presence of atelectasis and putrid secretions the sulfonamides were much less efficient than they were in simple bronchiectasis. Tolerance was about as expected except in cases known to be clinically allergic. Oatway states that there is no reason to believe that the structure of the bronchiectatic lesion changes, although its progress may be prevented by sulfonamide treatment. It is recommended that sulfonamides be used in nonsurgical cases and for preoperative therapy. They should be combined with postural drainage, bronchoscopic aspiration, climatotherapy and treatment of the sinuses.

According to Alexander,<sup>7</sup> the safety of pulmonary lobectomy has solved the problem of treatment for approximately half the bronchiectasis patients. Postural drainage is the most valuable of the nonsurgical therapeutic measures, but it is usually employed inefficiently. Every bronchiectatic patient should have at least one bronchoscopic examination, not only because some otherwise undetectable, important intrabronchial lesion may be discovered but also because the aspiration of secre-

tions and the chemical shrinkage of the bronchial mucosa often bring about improvement in the symptoms, which in occasional cases—notably in children but also in adults—is astonishing. Bronchoscopy is also of great value in preventing the development of bronchiectasis in early cases of pneumonitis of so-called “unresolved pneumonia.” The ordinary bronchoscopic treatment, in which a few of the secretions are aspirated and the mucosa is treated for only a few moments, is of little value. An effective treatment, which should be immediately preceded by a postural drainage that may occupy from fifteen to thirty minutes, requires that the bronchi containing secretions be repeatedly aspirated until all free secretions have been removed, both before and after the mucosa has been shrunken and the patient has repeatedly coughed on command, and that equal parts of 2 per cent pontocaine and 1:1000 epinephrine solutions, or other shrinkage drugs, be directly applied, step by step, to all parts of the mucosa that are swollen, the excess of the solution in the gauze pledgets being squeezed into those bronchi of the affected parts of the lung that are too small to be directly reached by the pledgets, or a small amount of the solution being injected into these bronchi. The effect of this treatment is to empty and open the choked bronchi, most of which, including the bronchiectases themselves, are distal to the field of bronchoscopic vision. The small bronchi in the peripheral portion of the bronchiectatic lobes cannot be reached by the bronchoscopic aspirator, but they can be at least partially emptied of secretions by voluntary coughing after all secretions proximal to them have been aspirated. Air enters more and more deeply into the lung as the secretions are aspirated and coughed from the bronchopulmonary areas that had been drowned in secretions.

Alexander believes that aeration of the peripheral portions of the affected lobes is the most important objective of bronchoscopic treatment. Aeration of the small bronchi and alveoli is the most effective means of aiding the patient to evacuate additional secretions by coughing, both during and following bronchoscopy. Deep breathing and coughing at fifteen-minute to sixty-minute intervals during waking hours for one or two days after a bronchoscopic treatment and the faithful carrying out of postural drainages indefinitely after bronchoscopy are obviously helpful in maintaining aeration and maximal evacuation of secretions. Evidence that a choked portion of a lung has been drained and aerated is often furnished by the change from dullness to resonance, from distant or almost absent breath sounds to distinct breath sounds and from few or no rales to many rales, as a result of a particularly effective bronchoscopic treatment, and sometimes solely as a result of postural drainage. The length of time during which aeration and drainage are maintained probably depends in part on the

heart and the opposite lung should be essentially normal. Probably few patients beyond sixty-five years of age are suitable for operation, although occasionally patients up to seventy years of age have been successfully operated on. Age alone does not necessarily contraindicate surgical intervention provided that the patient's general condition otherwise warrants it. He adds that, unfortunately, carcinoma of the lung tends to metastasize early and widely. In the series studied by Tinney,<sup>15</sup> metastatic lesions had been found in almost every part of the body. Every attempt to rule out the presence of metastatic carcinoma should be made. Involvement of nerves, such as the recurrent laryngeal or phrenic nerve, involvement of the brachial plexus or any indication of nerve injury usually means inoperability, as does also pleural effusion, particularly if it is bloody. The patient should not be denied thoracic exploration if a reasonable chance exists that the lesion can be removed. Too often it is found at the time of operation that the lesion has spread beyond operable limits. The resectability rate at the time of thoracic exploration, however, is about the same as that in cases in which exploration is performed for carcinoma of the stomach.

Pohle and Siris<sup>18</sup> believe that there is no question regarding the palliative value of cautiously applied x-ray therapy in the treatment of carcinoma of the bronchus. In rare cases, even in the presence of metastases, a five-year survival may be achieved.

Fermont<sup>19</sup> reports a seven-year cure in a case of carcinoma of the bronchus treated by radon seeds inserted through the bronchoscope. The growth was found by bronchoscopy to be obstructing the dorsal division of the bronchus of the right lobe. Biopsy showed squamous-cell carcinoma. Six and a half years after the treatment, the patient was readmitted, at which time bronchoscopy showed a slight general constriction of the bronchus of the right lower lobe at the level of the middle-lobe orifice. Biopsy showed no evidence of growth. The patient improved on conservative treatment and was able to resume his work. I cannot help wondering in this case whether the tumor was not in all probability an adenoma, rather than a carcinoma, for it has been noted elsewhere in this review, as well as previously, that sometimes a pathologist is unable to make the differential diagnosis between adenoma and carcinoma on a small bronchoscopic biopsy.

Rienhoff<sup>20</sup> has evaluated the present status of primary carcinoma of the lung. In his experience, second to the roentgenogram in importance in yielding information that is helpful in arriving at a definite diagnosis is bronchoscopy. In fact, either by direct vision or biopsy or both, a positive diagnosis of primary carcinoma of the lung can be made only in this manner. In 61 per cent of the patients in this series a bronchiogenic carcinoma was seen by this method and a positive biopsy specimen was

secured. In 39 per cent the bronchoscopy was negative. He quotes Graham as having been able to establish a positive diagnosis in 75 per cent of the cases in his series and states that Ochsner believes that positive bronchoscopy parallels hilar involvement in 70 to 85 per cent of cases. A pulmonary growth in the periphery or even hilar lesions confined to the upper lobes may be beyond the vision of the bronchoscopist. Valuable information can be elicited by bronchoscopy even when the growth cannot be seen, such as fixation or deformity, or both, owing to pressure on any visible portion of the bronchial tree. The presence of blood or purulent discharge from certain bronchi serves as a lead. In this series of cases there were no untoward results during or after bronchoscopies, and in the hands of experts Rienhoff believes that the patients have little if any discomfort. In conclusion he states that primary carcinoma of the lung, otherwise a fatal disease, can be satisfactorily treated by surgical removal of the entire organ. Surgical measures short of total pneumonectomy are not efficacious. Postoperative mortality and longevity are at least as good as, if not better than, the postoperative results following the surgical treatment of carcinoma of other organs.

### *Tuberculosis*

Of 115 cases of active pulmonary tuberculosis studied by Huang<sup>21</sup> at autopsy, 43 per cent showed evidence of tracheobronchial tuberculosis. This author believes that all bronchial tuberculosis is secondary to pulmonary tuberculosis. Direct implantation of tubercle bacilli from open cavities of the lungs to the mucous membrane or mucous glands seems to be the most plausible explanation for the majority of cases. Tuberculous ulceration is the predominating lesion of the respiratory tract in fatal cases.

Salkin, Cadden and Edson<sup>22</sup> examined bronchoscopically 622 cases of pulmonary tuberculosis. Ten per cent showed a tuberculous lesion on the first examination, and another 5 per cent eventually showed positive bronchial findings. The cases with a positive sputum and a cavity had an incidence three times as high as that of those with a negative sputum and no cavity. Tuberculosis of the lower lobe showed three times as much bronchitis as did that of the upper lobe. This phenomenon may be due to the greater endoscopic visibility of the lower-lobe bronchus and the stagnation of positive sputum there. One can expect a greater incidence of tracheobronchial tuberculosis in cases with laryngeal tuberculosis, and the reverse is also true. In over two thousand bronchoscopies in this study, only 1 case showed a spread of the disease that might be attributed to the procedure. Three or 4 per cent of the cases showed a drop in a previously existing fever, apparently owing to the greater ease of expectoration and improved aeration. Quite a number



nodes. Postoperative convalescence was uneventful. The patient did not give any preliminary history of a foreign body, but following the biopsy, further questioning revealed that about six years previously he had lost a small metal crucifix, which he thought that he had swallowed.

Fisher<sup>13</sup> states that carcinoma of the trachea is rare. It usually arises in the lower third of the trachea and is of the squamous-cell type. It is a highly malignant growth that develops insidiously. The diagnosis of tracheal neoplasm can be made only by direct tracheoscopy and removal of a piece of the tissue for microscopic study. There seems to be only one satisfactory type of treatment in these cases. This consists of electrocoagulation of the growth through the bronchoscope, with the tumor under direct vision. The electrocoagulation should be followed by irradiation of the tumor with roentgen rays of high voltage.

Pierson<sup>14</sup> reports a case of primary carcinoma of the trachea treated with radium. A man of sixty-one who had intermittent bouts of severe cough, dyspnea, suffocation and moderate hemoptysis for three years was found to have a primary adenocarcinoma of the trachea. An attempt to prove its histogenic origin from aberrant thyroid tissue by the use of radioactive iodine was unsuccessful. After removal of as much as possible of the tumor through the bronchoscope, the remnant was treated by radium applied within the trachea. Two years after treatment there were no subjective or objective evidences of tumor.

In a symposium on bronchiogenic carcinoma, Tinney<sup>15</sup> discusses the clinical features, remarking that, unfortunately, bronchiogenic carcinoma does not have characteristic symptoms. The symptoms are the same as those produced by any pulmonary inflammatory disease and depend essentially on the size and location of the tumor. Cough was an early symptom in 81 per cent of the cases in Tinney's series. Dyspnea in cases of bronchiogenic carcinoma is caused either by obstruction of the bronchial lumen and atelectasis or by development of pleural effusion. When dyspnea is associated with wheeze, an incorrect diagnosis of asthma is often made. Hemoptysis occurred in 53 per cent of the cases. Because of hemoptysis a number of patients were erroneously thought to have pulmonary tuberculosis. Pain occurred in 54 per cent of the cases. Loss of weight was noted in 71 per cent but is of no significance for early diagnosis. Although hoarseness was noted in only 8 per cent of the cases, it is an important symptom, because it means that the lesion is inoperable, having spread to the mediastinum, with involvement of the recurrent laryngeal nerve. There were no symptoms referable to the respiratory system in 5 per cent of the cases. The lesions were discovered in this group during a general physical examination that included a roentgenogram of the thorax. In 70 per cent of

the cases, — those in which an adequate follow-up study was available, — the average duration of life after the diagnosis was established was six months. The average duration of life from the onset of symptoms was fourteen and a half months. This deplorable delay in diagnosis is the most significant factor in the poor prognosis of bronchiogenic carcinoma. In this series the prognosis was not influenced by the type or grade of tumor.

Moersch<sup>11</sup> discusses the diagnostic aspects of bronchiogenic carcinoma, pointing out that a negative roentgenogram of the thorax does not rule out cancer of the lung. He therefore believes that it is important to remember that if a patient gives a history suggestive of carcinoma of the lung, even though the physical findings and roentgenograms of the thorax are essentially negative, further diagnostic procedures are justified. Bronchoscopy is one of the most important aids to diagnosis of carcinoma of the lung and offers the easiest and probably the most accurate method of early diagnosis. In 92 per cent of the cases in which bronchoscopy was performed, the diagnosis was made from tissue obtained through the bronchoscope.

Brindley<sup>16</sup> reports on the surgical aspects of bronchiogenic carcinoma, giving the results of pneumonectomy in 43 cases and lobectomy in 2. Seven patients (16 per cent) died in the first twenty-four hours after operation; 7 additional patients died in the hospital after the operation. One patient died three months after the pneumonectomy was performed. One patient is known to have had a recurrence of the tumor in the pleura nine months after operation. No correspondence or further examination was obtained in 4 cases. All the other patients were alive and without known recurrence of the lesion when last heard from or at the time of their last examination.

In a discussion of this symposium on bronchiogenic carcinoma, Clagett<sup>17</sup> notes that improved results from the surgical treatment of carcinoma of the lung must come — as they must for carcinoma in all locations of the body — from earlier diagnosis of the disease. Competent surgeons should not hesitate to perform an exploratory operation on the thorax. During the summer of 1943, Clagett performed pneumonectomy in at least 5 cases in which a positive diagnosis was not made beforehand, and in every one the suspected carcinoma was found and the lesion was removed. If he had awaited a positive diagnosis in these cases, the lesions would have become inoperable. He states that it is impossible to lay down any hard and fast rules to govern indications for thoracic exploration in cases of proved or suspected carcinoma of the lung. There should be roentgenographic and bronchoscopic evidence of a pulmonary lesion, and every attempt should be made to rule out other pulmonary conditions, such as lung abscess, bronchiectasis and tuberculosis. The patient should be in good general condition; the

### *Bronchoscopy in the Armed Forces*

In a report on the trends and practices in thoracic surgery in the Mediterranean theater, Churchill<sup>25</sup> has found bronchoscopic or catheter tracheo-bronchial aspiration increasingly useful to clear the respiratory passages of blood and secretions. Unless this is done, he says, oxygen administration and transfusion are of little avail.

### *Postoperative Use of the Bronchoscope*

Garlock<sup>26</sup> emphasizes the importance postoperatively of employing bronchoscopy to relieve the patient of tenacious secretions. He considers that it is often a lifesaving procedure.

### *Postlobectomy Lobar Collapse*

Sampson and Collis<sup>27</sup> believe that bronchoscopy is important in postlobectomy lobar collapse. In practice they have found that only one bronchoscopy is required in adults, although recollapse may occur in children, necessitating further instrumentation. It was found that even on the first or second postoperative day these patients stood bronchoscopy without being upset; in fact, many immediately felt better. The procedure was always done in the operating room under a local anesthetic. By laying the patient on the unaffected side the bronchoscope could be introduced through the side of the mouth into the affected lung with remarkable ease. In fact, it was these authors' experience that it is easier to use the bronchoscope on these patients than on the usual run of patients. This is thought to be due to the greater ease with which they can relax. Sampson and Collis conclude that from several aspects postlobectomy lobar collapse is a serious complication; that it is due to the obstruction of the bronchi with pus in association with certain mechanical alterations in the shape of the bronchial tree after lobectomy; that the longer this pus is left plugging the bronchi, the deeper it will pass into the lung and the more permanent will be the condition; that once collapse occurs it should be treated immediately by bronchoscopic aspiration, the results of which are highly satisfactory; and that postural measures give rise to some hope of reducing the incidence of the condition.

### *Lung Abscess*

Brantigan and Looper<sup>28</sup> studied 122 cases of lung abscess, collecting from the literature 34 cases of patients who had received primary lobectomy for lung abscess. There were 7 deaths. The technic of Churchill<sup>29, 30</sup> was used. Preoperative preparation included diet, bronchoscopic drainage, chemotherapy and blood transfusion.

### *Hemoptysis in Mitral Stenosis*

Ferguson, Kobilak and Deitrick<sup>31</sup> believe that mitral stenosis causes dilatation of the bronchial

veins in the submucosa of the larger bronchi as a result of the establishment of a collateral flow through them. In mitral stenosis, when infarction and acute pulmonary edema are not present, hemoptysis is probably due to bleeding from these dilated veins. Eleven cases of rheumatic heart disease studied by a special method of injection of particulate matter into the pulmonary veins indicated the presence of direct venous connections between the bronchus and pulmonary veins in men of all ages.

### *Agenesis of Lung*

Valle and Graham<sup>32</sup> report a case of agenesis of the lung proved during life by exploratory operation, and another case not proved but with an almost certain diagnosis. In the first case, bronchoscopy showed a normal larynx and a trachea twisted and distorted and shifted toward the left. The left main stem bronchus was completely obstructed 2 cm. below the carina. A blind pocket at the end of this bronchus appeared to be covered with epithelium, and there was no definite evidence of tumor. The right bronchial tree was normal. Thoracotomy showed that the only vestige of the left lung was a short bronchial stump with no lung tissue. The thymus gland was absent. No abnormalities were noted, and the chest was closed. In the second case, the trachea was displaced to the left. The right bronchial tree was seen to be normal but the left main bronchus was completely obstructed about 1 cm. below the carina. In a discussion of the 38 proved cases reported in the literature, Valle and Graham say that bronchoscopic studies will reveal a block of the main stem bronchus a short distance from the carina provided a rudimentary main stem bronchus is present on the affected side. In the literature most of the cases were diagnosed after death, but this is probably due to the fact that the majority were reported before the bronchoscope and bronchograms were so widely used, or used at all, in the diagnosis of chest lesions. At present, exploratory thoracotomy, which can be performed quite easily and without too much risk for the patient, is a possible means of positively diagnosing this condition. The authors give a valuable table of the findings in these 38 cases. It is worthy of note that both their patients are still alive. One case, that of a forty-one-year-old woman, was proved by an exploratory thoracotomy after a clinical diagnosis had been made of massive atelectasis of the left lung due to complete block of the left main bronchus. The other case, that of a five-year-old boy, is presumed to have been agenesis of the lung since the physical examination showed asymmetry of the chest, absence of breath sounds and flatness to percussion on the left side. Also, the x-ray picture showed complete opacity on the left with displacement of the trachea toward that

of patients asked for another bronchoscopy because they thought that it facilitated expectoration, lessened cough and improved breathing. The use of local therapy in bronchitis is one of the most debatable points of the entire subject. The experience of these authors leads them to believe that local treatment is of value, but one must remember that about three fourths of all cases heal spontaneously if the disease in the parenchyma is controlled. Treatment should be especially applied to the remaining patients, who do not do well when the parenchymal lesion is inactivated or when such complications occur as an undesirable stenosis, an accessible focus of hemorrhage, severe cough, difficulty in expectoration or attacks of dyspnea. Cases with tracheobronchial tuberculosis show a severer clinical course and have a poorer prognosis than do those with normal bronchi.

In contrast to the findings of the above authors, Radner<sup>23</sup> has noted a number of postbronchoscopic reactions in pulmonary tuberculosis. He concludes as follows:

The subject of tuberculous tracheobronchitis is of tremendous interest to the phthisiologist and thoracic surgeon. The trend toward routine bronchoscopic examination of all patients admitted to the sanatorium is not without its disadvantages. Limitation of bronchoscopy to the indications described will suffice to take care of almost all cases requiring treatment. Eleven cases have been collected from the American literature in which spread of disease following bronchoscopy is mentioned. Not in all instances did the authors feel definitely that bronchoscopy was directly responsible for the spread. In a study of one hundred and eighty-three bronchoscopic examinations made on patients with pulmonary tuberculosis the following findings were obtained, indicating that bronchoscopy is not an innocent procedure: (1) Eighteen bronchoscopic examinations were followed by immediate post-bronchoscopic fever, to which little significance can be attached. (2) Twenty-six bronchoscopic examinations were followed by a secondary rise in temperature, appearing between the tenth and sixteenth postbronchoscopic day, lasting fourteen to twenty-one days. (3) Twenty-one bronchoscopies were followed by minimal infiltrative spread as seen on roentgen films. (4) Five bronchoscopic examinations were followed by atelectasis of a lobe or lung. In this series, the number of patients who developed fever and spread of lesions following bronchoscopy is beyond explanation by coincidence. As a result of these findings it is suggested that: (1) Patients bronchoscoped prior to thoracoplasty should have their examination preferably three weeks in advance with a new roentgen film of the chest before surgery. This will eliminate some of the post-operative spreads that may be seen following thoracoplasty which are unjustifiably attributed to surgery. (2) The interval between bronchoscopic examination or treatments should not be less than six or eight weeks to allow for subsidence of any reaction resulting from previous treatments. (3) The disturbance of the cough reflex is very likely associated with the febrile reaction and extension of disease reported above. To minimize this, prebronchoscopic medication should preferably be limited to short-acting drugs and intratracheal anesthesia avoided whenever possible.

Davies<sup>24</sup> in a discussion of the treatment of tracheobronchial tuberculosis states that the aim of local treatment is twofold: first, to promote the healing of ulcerations in the tracheobronchial tree; and second, to prevent or minimize stenosis. He believes that the silver nitrate cautery aids in the healing of tuberculous ulcers in the human bronchi and

trachea by preparing the ulcer base to receive and support the ingrowing epithelium. This may perhaps be accomplished by reducing granulations and combating secondary infection. He does not believe that it has anything to do with the tuberculous nature of the lesion. Since silver nitrate has been widely and successfully used for many years to promote healing of dirty, granulating, superficial ulcerations in other parts of the body, it is not surprising that it should be effective in the treatment of similar lesions in the tracheobronchial tree. The epithelialization of tracheobronchial ulcers is important in that it removes one and often the only source of bacilli in the sputum, thus preventing bronchiogenic dissemination of tuberculosis and further bronchial or tracheal infection by implantation. It is also evident that epithelialization prevents a further increase in the size and extent of the ulcer. This may be helpful in preventing a localized ulcer from eventually involving the whole circumference of the bronchial lumen. In the bronchus, as in other hollow organs, circumferential ulceration is likely to be followed by serious stenosis, because of the concentric contraction of the fibrous tissue that is laid down as part of the repair process. It is Davies's opinion, however, that in 19 of his 26 cases local therapy was of considerable importance. In 2 of the remaining 7 cases, which were seen early in the course of the study, the local therapy employed was grossly insufficient by his present standards, only 10 per cent silver nitrate having been used, and that at intervals of a month or six weeks. Those collected cases in which local therapy was not used showed 31 (26 per cent) of 121 patients dead and 13 cases (11 per cent) classified as "healed," "well" and so forth. Combination of Davies's results with those collected from the literature in which local therapy was used shows 83 (39 per cent) of 215 cases "arrested," "healed" or "well" and 29 patients (13 per cent) dead. There is less than one chance in two thousand, considering arrested cases, and less than one chance in two hundred, considering deaths, that such a difference in results is solely accidental. The author advises the following treatment: complete bed rest in a sanatorium and a diet adequate in all essentials; relief of symptoms by a warm, humid atmosphere, adequate fluid intake, postural drainage and the use of expectorants, antispasmodics and barbiturates as necessary; persistent bronchoscopic cauterization of all accessible ulcerated lesions at biweekly intervals, preferably with a 30 per cent solution of silver nitrate; use of collapse therapy if the parenchymal lesion by itself demands collapse or if a main or lobar bronchus is seriously obstructed and if the obstruction cannot be promptly relieved; complete thoracoplasty as the procedure of choice if collapse is indicated; and in a few exceptional cases, lobectomy, pneumonectomy or open-cavity drainage when more conservative measures have failed.

## MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE COUNCIL

Special Meeting, January 31, 1945

A SPECIAL meeting of the Council of the Massachusetts Medical Society was called to order at 10:30 a.m. in John Ware Hall, 8 Fenway, Boston, on Wednesday, January 31, 1945, by the president, Dr. Elmer S. Bagnall, Essex North; 207 councilors were present (Appendix No. 1).

The record of the meeting held on October 4, 1944, as published in the *New England Journal of Medicine*, issue of December 21, 1944, was presented by the Secretary. On a motion by Dr. John B. Hall, Norfolk, and a second by Dr. David Cheever, Suffolk, the record was approved by vote of the Council.

## REPORT OF EXECUTIVE COMMITTEE

This report was presented by the Secretary. He said that the committee had reviewed a "basic general plan for a Massachusetts program for the care of children with acute rheumatic fever" as presented by the Committee on Public Health. He added that this plan was presented in detail in the circular of advance information, which had been sent to each councilor. He said that the committee recommended the approval of this report provided certain qualifications which had to do with those permitted to act as consultants under the plan be deleted. These qualifications were represented by the following words which appeared in that part of the report which referred to this subject: "who are certified by or eligible for certification by the boards of their respective specialties."

The Secretary spoke of a communication which the committee had received from Dr. Jacob Fine, in which the latter sought to have adopted the following amendment to the by-laws of the Massachusetts Medical Society:

Chapter V, Section 2b, is hereby amended to read as follows:

The Secretary of a District Society shall receive an application from a graduate of a discontinued medical school, a foreign medical school after the year 1933 or any medical school not approved by the Council only when the applicant has possessed a license to practice medicine in the United States or its territories for at least five years. A graduate of a foreign medical school on the approved list of the National Board of Medical Examiners prior to 1934 may apply for membership to the secretary of a district society if he has possessed a license to practice medicine for a minimum of five years.

He called attention to Dr. Fine's argument in support of this proposal as it appeared in the circular of advance information (Appendix No. 2).

In connection with the administrability of the proposed amendment the Secretary read the following letter from Mr. Everett S. Elwood, executive

secretary of the National Board of Medical Examiners:

Dear Dr. Tighe:

The only list of the European medical schools that the National Board ever had has been the list prepared by the Examining Board in England. As you know, there has never been an appraisal of the medical schools in Europe by any accredited agency in this country. Dr. Rappleye, dean of the Columbia University Medical School, brought back some information about the so-called "extramural schools" of Scotland and Ireland which indicated that they were not up to the standards set for the approved schools in this country and we therefore discontinued accepting their graduates after 1939, as the enclosed resolution will show. With this exception, our board has used the list of schools that were approved for admission to the examinations of the English Board, and until we stopped admitting graduates from the Continental schools of Europe we admitted to our examinations those whose credentials were satisfactory, if they had completed their work satisfactorily in a European school on the list of the English Board.

Your letter asks for a list before 1934. I enclose an extra copy, that we had on hand, of the pamphlet gotten out by the English Board in 1934. If I knew the particular school or schools to which you refer I could probably reply more satisfactorily.

Very sincerely yours,  
EVERETT S. ELWOOD, *Executive Secretary*  
National Board of Medical Examiners

December 21, 1944

The Secretary added that the committee unanimously recommended that the Council disapprove Dr. Fine's amendment. He moved the adoption of this recommendation. The motion was seconded by Dr. Cheever, and it was so ordered by vote of the Council.

The Secretary spoke of a communication which had been received by the committee from Dr. Sidney C. Wiggan in which the latter requested that the Massachusetts Medical Society set up a Section of Anesthesiology. He referred the Council to this letter as published in the circular of advance information. He said that the committee looked favorably on this petition and recommended to the Council that such a section be set up. He moved the adoption of the recommendation. This motion was seconded by Dr. Peirce H. Leavitt, Plymouth, and it was so ordered by vote of the Council.

The Secretary said that the committee had reviewed the report of the Committee on Public Relations and approved the recommendations contained in this report.

He said that the committee had reviewed the report of the Committee Appointed to Confer with the Massachusetts Hospital Association and recommended to the Council that this report be referred back to its source for clarification.

The Secretary said that the committee noted that the President had created a Committee on Council

side, and the bronchogram a complete block of the left main bronchus. A bronchoscopy was performed that confirmed these findings.

### *Lung Changes in Electric Arc Welders*

According to Sander,<sup>33</sup> it has become generally recognized that both acute and chronic lung changes may occur when welders are exposed to highly concentrated fumes. Sander discusses 4 cases, stating that he has not found any remarkable degree of bronchitis in welders generally, even including those who have obviously had intense fume exposures.

I recently had the opportunity to do a bronchoscopy on a patient exposed to the fumes of electric arc welding and found a slight chronic bronchitis. Following bronchoscopy the patient was completely relieved of his former symptoms, namely, sensation of a lump and irritation in throat, cough, wheeze, dyspnea and choking. He was convinced that the bronchoscopy had cured him. It is my opinion, however, that elimination of welding fumes is the real reason that he feels so well at the present time.

Sander concludes as follows: Electric arc welding that is done in large rooms and where the fumes are not allowed to concentrate excessively near the breathing level does not cause any lung changes, even after many years of work. Excessive inhalation of concentrated fumes, especially in confined and unventilated spaces, may cause siderosis in the lungs in six to ten years. The siderosis so produced consists only of inert iron-pigment deposits in the lymphatics, without proliferation of fibrous tissue and without progressive changes after exposure is materially decreased. This siderosis does not predispose to tuberculosis or other lung infections, nor does it cause functional impairment of the lungs and therefore symptoms referable to the lungs. Acute irritative phenomena of the throat may occur with too prolonged confined work in dense clouds of fumes, but these appear to be transitory reactions leaving no residual impairment. Any respiratory involvement may be prevented in welding, even with the most confined and prolonged work, if proper precautions are taken, either by adequate exhaust ventilation, ventilated helmets or positive-pressure respirators.

(To be concluded)

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## MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE COUNCIL

Special Meeting, January 31, 1945

A SPECIAL meeting of the Council of the Massachusetts Medical Society was called to order at 10:30 a.m. in John Ware Hall, 8 Fenway, Boston, on Wednesday, January 31, 1945, by the president, Dr. Elmer S. Bagnall, Essex North; 207 councilors were present (Appendix No. 1).

The record of the meeting held on October 4, 1944, as published in the *New England Journal of Medicine*, issue of December 21, 1944, was presented by the Secretary. On a motion by Dr. John B. Hall, Norfolk, and a second by Dr. David Cheever, Suffolk, the record was approved by vote of the Council.

## REPORT OF EXECUTIVE COMMITTEE

This report was presented by the Secretary. He said that the committee had reviewed a "basic general plan for a Massachusetts program for the care of children with acute rheumatic fever" as presented by the Committee on Public Health. He added that this plan was presented in detail in the circular of advance information, which had been sent to each councilor. He said that the committee recommended the approval of this report provided certain qualifications which had to do with those permitted to act as consultants under the plan be deleted. These qualifications were represented by the following words which appeared in that part of the report which referred to this subject: "who are certified by or eligible for certification by the boards of their respective specialties."

The Secretary spoke of a communication which the committee had received from Dr. Jacob Fine, in which the latter sought to have adopted the following amendment to the by-laws of the Massachusetts Medical Society:

Chapter V, Section 2b, is hereby amended to read as follows:

The Secretary of a District Society shall receive an application from a graduate of a discontinued medical school, a foreign medical school after the year 1933 or any medical school not approved by the Council only when the applicant has possessed a license to practice medicine in the United States or its territories for at least five years. A graduate of a foreign medical school on the approved list of the National Board of Medical Examiners prior to 1934 may apply for membership to the secretary of a district society if he has possessed a license to practice medicine for a minimum of five years.

He called attention to Dr. Fine's argument in support of this proposal as it appeared in the circular of advance information (Appendix No. 2).

In connection with the administrability of the proposed amendment the Secretary read the following letter from Mr. Everett S. Elwood, executive

secretary of the National Board of Medical Examiners:

Dear Dr. Tighe:

The only list of the European medical schools that the National Board ever had has been the list prepared by the Examining Board in England. As you know, there has never been an appraisal of the medical schools in Europe by any accredited agency in this country. Dr. Rappleye, dean of the Columbia University Medical School, brought back some information about the so-called "extramural schools" of Scotland and Ireland which indicated that they were not up to the standards set for the approved schools in this country and we therefore discontinued accepting their graduates after 1939, as the enclosed resolution will show. With this exception, our board has used the list of schools that were approved for admission to the examinations of the English Board, and until we stopped admitting graduates from the Continental schools of Europe we admitted to our examinations those whose credentials were satisfactory, if they had completed their work satisfactorily in a European school on the list of the English Board.

Your letter asks for a list before 1934. I enclose an extra copy, that we had on hand, of the pamphlet gotten out by the English Board in 1934. If I knew the particular school or schools to which you refer I could probably reply more satisfactorily.

Very sincerely yours,

EVERETT S. ELWOOD, *Executive Secretary*  
National Board of Medical Examiners

December 21, 1944

The Secretary added that the committee unanimously recommended that the Council disapprove Dr. Fine's amendment. He moved the adoption of this recommendation. The motion was seconded by Dr. Cheever, and it was so ordered by vote of the Council.

The Secretary spoke of a communication which had been received by the committee from Dr. Sidney C. Wiggin in which the latter requested that the Massachusetts Medical Society set up a Section of Anesthesiology. He referred the Council to this letter as published in the circular of advance information. He said that the committee looked favorably on this petition and recommended to the Council that such a section be set up. He moved the adoption of the recommendation. This motion was seconded by Dr. Peirce H. Leavitt, Plymouth, and it was so ordered by vote of the Council.

The Secretary said that the committee had reviewed the report of the Committee on Public Relations and approved the recommendations contained in this report.

He said that the committee had reviewed the report of the Committee Appointed to Confer with the Massachusetts Hospital Association and recommended to the Council that this report be referred back to its source for clarification.

The Secretary said that the committee noted that the President had created a Committee on Council

Rules. He reported that the Executive Committee approved of this act of the President and recommended that the Council do likewise. He moved the adoption of this recommendation. This motion was seconded by Dr. Guy L. Richardson, Essex North, and it was so ordered by vote of the Council.

He said that the Executive Committee had reviewed the report of the Committee on Council Rules and approved the recommendations contained therein, seeing in these recommendations a means of shortening, facilitating and making more orderly the conduct of the business of the Council.

He said the Executive Committee had reviewed the report of the Committee on Maternal Welfare and approved it.

He next reported on the questionnaire concerning the establishment of a Postwar Loan Fund for the use of those of our members after their retirement from the armed services. He said that 4609 questionnaires of the following character were sent out:

#### THE POSTWAR LOAN FUND

1. The only objective of the Postwar Loan Fund is to make available immediate financial assistance to those members of the Massachusetts Medical Society who, having served in the present World War, on separation from the service, are in need of temporary financial aid.

2. To establish this fund it is proposed to levy an assessment on all those members of the Society not privileged to serve in the armed forces during this War. While the amount of the levy and its duration will be determined by the Council of the Massachusetts Medical Society, the Committee on Postwar Loan Fund has recommended that this fund be raised by an assessment of \$10.00 on all the members heretofore described. It is to be understood that this assessment will have the same force as any assessment authorized by the Council in accordance with the by-laws of the Society.

3. The procedure of application to the fund will be simple and will entail no endorses. The interest charge will be nominal. It will also be confidential between the applicant and a committee, to be appointed by the President.

4. In establishing such a plan we shall be privileged to serve those of our members who are serving us during these trying days.

5. Please indicate your opinion with reference to this fund on the space below, and mail it immediately, certainly on or before December 10, 1944.

#### PLEASE RETURN THIS BALLOT

I ☐ do  
☐ do not approve of the Postwar Loan Fund.

Name . . . . .

District . . . . .

No unsigned ballots will be counted. Your ballot is confidential.

He added that 1897 post cards had been returned: 1457, or 76.8 per cent, approved, 374, or 19.7 per cent, disapproved, and 66 were blank.

The Secretary, in continuing to refer to this matter, said that the Executive Committee noted that, in the report originally offered by the Committee on Postwar Loan Fund, no recommendations were made as to the final disposition of the monies raised under these auspices.

There were those, he added, who thought that such funds, after they had served the original purpose for which they had been gathered, might be used to set up in the Society a permanent benevolent fund for the purpose of easing the burden of those of the fellows, or of their dependents, who had fallen on evil times.

He said that the use of the Society's funds as a means of financing the enterprise proposed by the

Committee on Postwar Loan Fund was also discussed and that, although no conclusions were arrived at by the Executive Committee in these matters, it recommended to the Council that the report originally offered be referred back to the Committee on Postwar Loan Fund for recommendations with regard to them.

The Secretary said that the Executive Committee reviewed the report of the Committee on Finance and approved it subject to certain corrections, which had since been made.

He said that the Executive Committee reviewed the report of the Committee on Postwar Planning and approved it.

He said that the Council, at its meeting February 5, 1941, authorized a change in the type of diploma which is issued to those who become members of the Massachusetts Medical Society. This authorization assumed that the supply of diploma forms then on hand be used until exhausted, which point was about to be reached.

The Executive Committee had inspected the new diploma and did not believe that it represented an improvement on the old one. It was thought that the new form was not well balanced as a document and that it was devoid of artistic merit. The Executive Committee therefore recommended that the Council rescind its action of February 5, 1941, and that the old form be continued. The Secretary moved the adoption of this recommendation. This motion was seconded by Dr. Leavitt, and it was so ordered by vote of the Council.

He added that the committee had approved of certain *ad interim* appointments made by the President.

He moved the adoption of the report as a whole. This motion was seconded by Dr. Cheever, and it was so ordered by vote of the Council.

#### REPORTS OF STANDING COMMITTEES

*Committee on Publications* — Dr. Richard M. Smith, Suffolk, chairman.

This report (Appendix No. 3) was offered by the chairman, who expressed the committee's great sense of loss in the death of Dr. William B. Breed.

He said that the committee had invited Colonel Walter Bauer, medical consultant to the Eighth Service Command, to deliver the Shattuck Lecture and that the latter had accepted subject to exigencies of military duty.

He added that the committee recommended that a directory of the fellows of the Society be published in 1945, that the issue be limited to 500 copies and that not more than \$1500 be appropriated for this purpose.

Dr. Smith bespoke the committee's deep appreciation of the efficient manner in which the affairs of the *Journal* had been handled by the editor, Dr. Robert N. Nye. Miss Davies, the assistant editor,

and her assistants were also commended in the report.

Dr. Smith said that, during 1944, 6109 new "outside" subscriptions had been added and that this figure was 42 per cent greater than that of 1943. He said that 4221 of these were regular, and that 1888 were student subscriptions. He said that there were many cancellations but that the net increase was 2394 regular, and 357 student. He added, as being specially noteworthy, the fact that of the 1531 student subscriptions that had expired, 674 had been renewed at the full rate.

He said that, as of December 31, 1944, the *Journal* had 14,885 subscribers and that this did not include 337 copies that were sent once each month to the members of the New Hampshire Medical Society.

He said that the operations of the *Journal* during 1944 resulted in a net loss of \$7937, which is partly balanced by an appropriation of \$7900 from the Society. He added that the net cost to each member in 1944 was \$1.81 as compared with \$1.30 in 1943, and that this was so because of increased costs of printing and binding.

Dr. Smith said that 194 manuscripts had been considered by the Editorial Board during the year and that 151 were accepted. He added that the committee believed that a cut in pagination was more desirable than the acceptances of papers that do not meet the standards set by the board. He said that shortage of paper continues to represent a problem.

He spoke of the fact that a change had been made a year ago in the firm responsible for printing. It was hoped that this would overcome some of the difficulties that had been present in previous years. The problems, however, are still present, he added.

Dr. Smith spoke of a survey that had been conducted among the subscribers outside of Massachusetts for the purpose of determining the most popular features of the *Journal*. Those approached in this survey were also asked if they would subscribe to the progress reports if the latter were printed as a quarterly publication. Subscribers in Connecticut, Ohio, Texas, Oregon and Washington were polled. The majority indicated approval of the *Journal* because of its total content. The response to the question concerning the quarterly publication of the progress reports appeared to indicate that this would be a successful undertaking.

Dr. Smith said that the revenue from advertising during 1945 promises to be larger and that the net cost to the Society should be lower.

He added, finally, that the accounts of the *Journal* had been audited and found to be in order.

During the course of this report Dr. Smith showed a slide to illustrate certain facts contained in the report.

Dr. Smith moved the acceptance of the report and the adoption of the recommendations. This motion

was seconded by Dr. Cheever, and it was so ordered by vote of the Council.

*Committee on Arrangements* — Dr. Roy J. Heffernan, Norfolk, chairman.

This report, which was offered by Dr. Heffernan, is as follows:

The Committee on Arrangements has held a number of meetings throughout the fall and early winter. As a result of these conclaves a varied and interesting program has been arranged for the annual meeting on May 22, 23 and 24, at the Hotel Statler, Boston.

We have been particularly fortunate in securing the active co-operation of the medical departments of the United States Army. Three of our speakers are from the Surgeon General's office, and another is the director of the Army Pathological Museum. We feel that the program will be of interest to all the members of our society but particularly to the general practitioner, for whom it is pre-eminently planned.

The sale of space to technical exhibitors has exceeded all previous records. Ten thousand, six hundred and twenty dollars' worth of space have been sold, and over \$6451.50 is now in the hands of your treasurer. This splendid achievement is due almost entirely to the energetic efficient management of this department by Mr. Robert Boyd.

Your committee is, of course, aware of the recent ruling of the O. D. T. forbidding meetings not connected with the war effort. We have a strong conviction, however, that our annual meeting is justified in view of our close co-operation with the armed services and other governmental agencies, and because the need for postgraduate instruction and demonstration is greater at this time than ever before. In due time we shall apply for permission to hold the meeting in its regular form, and our future activities will be governed by the result of that application.

Dr. Heffernan moved the adoption of the report. This motion was seconded by Dr. Hall, and it was so ordered by vote of the Council.

*Committee on Ethics and Discipline* — Dr. Ralph R. Stratton, Middlesex East, chairman.

No report.

*Committee on Medical Education* — Dr. Robert T. Monroe, Norfolk, chairman.

No report.

*Committee on Membership* — Dr. Harlan F. Newton, Suffolk, chairman.

No report.

*Committee on Public Health* — Dr. Roy J. Ward, Worcester, chairman.

Dr. Ward offered the report (Appendix No. 4) as it appeared in the circular of advance information and moved the approval of the rheumatic-heart-disease program as submitted therein. This motion was seconded by Dr. Leroy E. Parkins, Suffolk.

Dr. Donald Munro, Suffolk, moved as an amendment the adoption of the recommendation of the Executive Committee. (This called for the approval of the report provided the following phrase was deleted: "who are certified by or eligible for certification by the boards of their respective specialties.") This amendment was seconded by Dr. Richardson.



Dr. Helen S. Pittman, Suffolk, asked why the Executive Committee recommended the deletion of this phraseology.

Dr. Munro replied that such boards were not sufficiently established in the eyes of the public at large and particularly in the eyes of the general practitioner, who sees the majority of the cases of rheumatic heart disease, to warrant limiting the choice of consultants to this group.

The amendment was adopted by vote of the Council.

Dr. Ward's motion to adopt the report, as amended, was likewise ordered by vote of the Council.

Dr. Ward said that Chapter VII, Section 11, of the by-laws of the Massachusetts Medical Society state that the Committee on Public Health "shall foster the knowledge of the prevention and treatment of disease by any appropriate measures." He added that, under this definition, his committee had felt justified in entering into a study of the matter of transfusions and that with this end in mind the following subcommittee had been appointed: William Dameshek, chairman, Geoffrey Edsall, William Freeman, Charles A. Janeway, George L. Schadt, George MacIver, Joseph Ross and Benjamin F. Andrews.

Dr. Ward submitted the following report issued by the subcommittee:

The first meeting of the Subcommittee on Transfusions of the Committee on Public Health was held on Wednesday, January 24, and was attended by Drs. William Dameshek, chairman, Geoffrey Edsall, William Freeman, Charles A. Janeway and Elmer S. Bagnall.

It was the opinion of the committee that a review of the transfusion situation in the Commonwealth was greatly to be desired, with particular reference to reactions, methods of typing and cross matching, the types of personnel involved and so forth. Having once obtained a general idea of these data by means of questionnaires, it might then be desirable for the Society to participate in an educational campaign, preferably with the collaboration of the Massachusetts Department of Public Health.

Educational features might include a rather detailed instruction booklet for use by hospital physicians and technicians, systematically conducted talks by lecturers familiar with the subject, and short one-day or two-day refresher courses for technicians, the latter perhaps with the collaboration of the Commonwealth Fund and the Commonwealth.

Dr. Edsall, representing the Department of Public Health, expressed his great interest in the objectives of the committee and welcomed its possible collaboration, particularly with respect to revision of the present regulations regarding transfusions, the standardization of typing serums and so forth. He believed that new regulations respecting transfusions and new developments relating to inspection and standardization of typing serums might well be a collaborative venture between the Massachusetts Department of Public Health on the one hand and the Massachusetts Medical Society, through this special subcommittee, on the other.

It was finally concluded that this committee might function in these four fields: the collection of information regarding transfusions, blood grouping tests and transfusion reactions; education of physicians and technicians by appropriate means; the development of facilities relating to typing serums and so forth; and the standardization of regulations relating to transfusions. All these functions might be made in collaboration with the Department of Public Health.

An appropriation of \$200 would probably be sufficient to defray printing and mailing costs, particularly for the proposed questionnaire.

Dr. Ward moved that, with the approval of the Committee on Finance, \$200 be added to the budget of the Committee on Public Health to provide for clerical help and postage for making this study. This motion was seconded by Dr. Richardson.

Dr. George Leonard Schadt, Hampden, was recognized by the chair. He prefaced his remarks by assuring the Council that there was nothing personal in what he was about to say. He pointed out that this matter was presented to the Council in October and defeated. He expressed surprise on the receipt of a letter from Dr. Ward saying that he, Dr. Schadt, had been appointed to a subcommittee of the Committee on Public Health which subcommittee would consider the matter of transfusions. He added that what he had to say might therefore be considered in the nature of a dissenting minority report.

He thought the setting up of a subcommittee by a committee of the Society in a matter that had been turned down by the Council was establishing a curious precedent. He expressed the thought that this was work that the Massachusetts Department of Public Health, and not the Massachusetts Medical Society, should engage in.

Dr. Dameshek explained that, during the luncheon period at the October meeting of the Council, Dr. Ward had approached him and suggested that the Committee on Public Health was interested in this sort of thing and further suggested developing a subcommittee of his committee to look into this matter. He said such a subcommittee was established. He said that he was at a loss to understand the reaction against this sort of subcommittee. He expressed it as his belief that the Massachusetts Medical Society should be concerned with better practices and with the education of physicians. He added that the Society should likewise be concerned with the development of new technics in hospitals and with more or less supervision of these technics.

He thought such a subcommittee could gather information concerning the preliminary steps that should be used to safeguard transfusions, that the committee might draw up standards that could be used to further safeguard this procedure, that these standards might be set forth in a booklet and that talks and refresher courses to physicians and technicians might further supplement the program.

He expressed the hope that the motion would prevail.

At that point, Dr. Charles E. Mongan, Middlesex South, asked two questions: "Is the transfusion of blood from one person to another a public-health function, and what is public health? Where does public health end and private health begin?" The President answered by saying that the questions flattered him.

Dr. Mongan moved that the matter be laid on the table. The motion was seconded by Dr. Lester M. Felton, Worcester, and it was so ordered by vote of the Council. This action was accomplished by a show of hands — 84 for the motion and 71 against.

*Committee on Society Headquarters* — Dr. Frank R. Ober, Suffolk, chairman.

This report (Appendix No. 5) was offered by Dr. Ober, who pointed out that more room will be needed for the facilities of the Society — notably for the information bureau and, as pointed out in Dr. Smith's report, for the *Journal*.

Dr. Ober moved the adoption of the report. This motion was seconded by Dr. Hilbert F. Dav, Middlesex South, and it was so ordered by vote of the Council.

*Committee on Medical Defense* — Dr. Arthur W. Allen, Suffolk, chairman.

No report.

*Committee on Finance* — Dr. Francis C. Hall, Suffolk, chairman.

This report (Appendix No. 6), as published in the circular of advance information and representing the budget for the year 1945, was presented by Dr. Hall, who moved its adoption. This motion was seconded by Dr. Cheever, and it was so ordered by vote of the Council.

*Committee on Industrial Health* — Dr. Dwight O'Hara, Middlesex South, chairman.

No report.

#### REPORTS ON STATE-WIDE COMMITTEES

*Committee on Legislation* — Dr. William E. Browne, Suffolk, chairman.

Dr. Browne announced that the holding of the Council meeting a week ahead of schedule had made a written report impossible.

Dr. Browne stated that Mr. Charles Dunn had been retained as counsel and that no contract had been entered into by the committee in this connection. He added that this left the committee free to make a change if it saw fit. He said that the committee was endeavoring to get the name of the family physician of each member of the Legislature and that some progress had been made in this direction.

Dr. Browne then spoke of Bill 261. He explained that this bill provided for a system of sickness insurance for those employed in industry. He added that the proposal would be compulsory from the standpoint of the employer and voluntary on the part of the employee and that the system thus set up would be administered by the Industrial Accident Board. He said that he had been informed by counsel that this bill was not in conflict with the

Blue Shield. He said that the committee was not prepared to advise with regard to this bill but that "by the time it comes up for discussion in the Senate and House, we shall know more about it and we trust that any action we may take will be worth while."

Dr. Browne next spoke of a bill sponsored by Dr. Leavitt, of Brockton. This bill, he added, had to do with the powers vested in medical examiners in the matter of autopsies. The proposed bill places the determination whether or not an autopsy shall be performed in the hands of the medical examiner. Dr. Browne said the committee approved the bill.

He spoke of a bill that would make cancer a reportable disease. He said that, although the bill was not without certain objections, he thought his committee would approve of it.

Dr. Browne next referred to House Bills 415 and 416 introduced on the petition of Dr. H. Quimby Gallepe. He said that, at its meeting held earlier in the day, the committee had voted to recommend to the Council disapproval of these bills. He explained that Bill 415 would forbid anyone to take the examinations given by the State Board of Registration in Medicine more than three times. He moved the adoption of this recommendation. This motion was seconded by Dr. Felton.

Dr. H. Quimby Gallepe, Middlesex South, explained reasons behind the two bills introduced by the Board of Registration in Medicine. He said that they were written by Dr. John Spellman for the purpose of obviating the practice of political pressure, which practice had placed past boards in trouble, and for the purpose of getting rid of those who obviously could never qualify. He said that only 40 per cent of those who took the examination in November passed and that the 60 per cent who failed comprised those who had taken the examination "over and over and over again." He said that Bill 416 would give the Board the right to examine a doctor whose license had been revoked and who had been away from the practice of medicine for a considerable time.

He added that Bills 415 and 416 were not important at the moment and that the Board would gladly set them aside if it could get complete support for the more important bills that were before the Legislature. He explained that the latter bills would tear down the Medical Practice Act and that, if their proponents were successful, Massachusetts would go back even beyond the unenviable position that she occupied previous to 1936. Finally, he urged the Council's support in defeating the bills introduced by the chiropractors, the osteopaths and those who favor substandard schools.

Dr. Browne agreed that the bills introduced by the Board might be considered at a later time.

Dr. Daniel B. Reardon, Norfolk South, said that his district was meeting with the legislators from that area on Thursday evening. He recommended this procedure to other districts.

Dr. Helen S. Pittman, Suffolk, asked why the Executive Committee recommended the deletion of this phraseology.

Dr. Munro replied that such boards were not sufficiently established in the eyes of the public at large and particularly in the eyes of the general practitioner, who sees the majority of the cases of rheumatic heart disease, to warrant limiting the choice of consultants to this group.

The amendment was adopted by vote of the Council.

Dr. Ward's motion to adopt the report, as amended, was likewise ordered by vote of the Council.

Dr. Ward said that Chapter VII, Section 11, of the by-laws of the Massachusetts Medical Society state that the Committee on Public Health "shall foster the knowledge of the prevention and treatment of disease by any appropriate measures." He added that, under this definition, his committee had felt justified in entering into a study of the matter of transfusions and that with this end in mind the following subcommittee had been appointed: William Dameshek, chairman, Geoffrey Edsall, William Freeman, Charles A. Janeway, George L. Schadt, George MacIver, Joseph Ross and Benjamin F. Andrews.

Dr. Ward submitted the following report issued by the subcommittee:

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*It was the opinion of the committee that a review of the transfusion situation in the Commonwealth was greatly to be desired, with particular reference to reactions, methods of typing and cross matching, the types of personnel involved and so forth. Having once obtained a general idea of these data by means of questionnaires, it might then be desirable for the Society to participate in an educational campaign, preferably with the collaboration of the Massachusetts Department of Public Health.*

*Educational features might include a rather detailed instruction booklet for use by hospital physicians and technicians, systematically conducted talks by lecturers familiar with the subject, and short one-day or two-day refresher courses for technicians, the latter perhaps with the collaboration of the Commonwealth Fund and the Commonwealth.*

*Dr. Edsall, representing the Department of Public Health, expressed his great interest in the objectives of the committee and welcomed its possible collaboration, particularly with respect to revision of the present regulations regarding transfusions, the standardization of typing serums and so forth. He believed that new regulations respecting transfusions and new developments relating to inspection and standardization of typing serums might well be a collaborative venture between the Massachusetts Department of Public Health on the one hand and the Massachusetts Medical Society, through this special subcommittee, on the other.*

*It was finally concluded that this committee might function in these four fields: the collection of information regarding transfusions, blood grouping tests and transfusion reactions; education of physicians and technicians by appropriate means; the development of facilities relating to typing serums and so forth; and the standardization of regulations relating to transfusions. All these functions might be made in collaboration with the Department of Public Health.*

*An appropriation of \$200 would probably be sufficient to defray printing and mailing costs, particularly for the proposed questionnaire.*

Dr. Ward moved that, with the approval of the Committee on Finance, \$200 be added to the budget of the Committee on Public Health to provide for clerical help and postage for making this study. This motion was seconded by Dr. Richardson.

Dr. George Leonard Schadt, Hampden, was recognized by the chair. He prefaced his remarks by assuring the Council that there was nothing personal in what he was about to say. He pointed out that this matter was presented to the Council in October and defeated. He expressed surprise on the receipt of a letter from Dr. Ward saying that he, Dr. Schadt, had been appointed to a subcommittee of the Committee on Public Health which subcommittee would consider the matter of transfusions. He added that what he had to say might therefore be considered in the nature of a dissenting minority report.

He thought the setting up of a subcommittee by a committee of the Society in a matter that had been turned down by the Council was establishing a curious precedent. He expressed the thought that this was work that the Massachusetts Department of Public Health, and not the Massachusetts Medical Society, should engage in.

Dr. Dameshek explained that, during the luncheon period at the October meeting of the Council, Dr. Ward had approached him and suggested that the Committee on Public Health was interested in this sort of thing and further suggested developing a subcommittee of his committee to look into this matter. He said such a subcommittee was established. He said that he was at a loss to understand the reaction against this sort of subcommittee. He expressed it as his belief that the Massachusetts Medical Society should be concerned with better practices and with the education of physicians. He added that the Society should likewise be concerned with the development of new technics in hospitals and with more or less supervision of these technics.

He thought such a subcommittee could gather information concerning the preliminary steps that should be used to safeguard transfusions, that the committee might draw up standards that could be used to further safeguard this procedure, that these standards might be set forth in a booklet and that talks and refresher courses to physicians and technicians might further supplement the program.

He expressed the hope that the motion would prevail.

At that point, Dr. Charles E. Mongan, Middlesex South, asked two questions: "Is the transfusion of blood from one person to another a public-health function, and what is public health? Where does public health end and private health begin?" The President answered by saying that the questions flattered him.

He moved the adoption of this recommendation. This motion was seconded by Dr. Cheever and it was so ordered by vote of the Council.

The second was as follows:

The secretary of the Society should instruct and encourage the executive secretary of the Society to familiarize himself with medical publicity.

Dr. Hornor moved the adoption of this recommendation. This motion was seconded by Dr. George J. Connor, Essex North, and it was so ordered by vote of the Council.

Dr. Hornor said that it was the unanimous opinion of the committee that the expense involved in the second recommendation should be charged to administration. He added that it was also the unanimous opinion of the committee that publicity for the annual meeting was the responsibility of the Committee on Arrangements.

Dr. Hornor moved the discharge of the Subcommittee to Look into the Matter of Better Publicity for the Massachusetts Medical Society. This motion was seconded by Dr. Richardson and it was so ordered by vote of the Council.

Dr. Hornor in offering the third recommendation reported the approval by the Committee on Public Relations of the following motion:

That the Committee on Public Relations of the Massachusetts Medical Society report to the Council of the Massachusetts Medical Society that this committee is in favor of finding and expanding common grounds of agreement with representative groups of the public and that a committee be appointed by the President with the end in mind of creating a better general understanding of the problems involved in good medical care.

He moved the adoption of the recommendation contained in this motion. This motion was seconded by Dr. Richardson, and it was so ordered by vote of the Council.

On behalf of the Committee on Public Relations Dr. Hornor moved the adoption of the fourth recommendation, which is as follows:

The Committee on Public Relations, recognizing the Society's obligation to further education of the public in regard to medicine, recommends to the Council that the president of the Society appoint a special committee, containing representatives of the Committee on Public Relations, Committee on Ethics and Discipline, Committee on Publications, Committee on Public Health and any others that he desires, to further the education of the public in regard to medical questions, particularly through popular magazines.

This motion was seconded by a councilor, and it was so ordered by vote of the Council.

Dr. Hornor said that the following questions concerning industrial accidents had been referred to a subcommittee headed by Dr. Ellison:

The abuse of the rules that an injured employee may have the services of a physician at his own choice.

The question of the correct charge by a doctor to a patient he treated, the case having previously been declined by the Committee on Ethics and Discipline.

The question of simplified insurance forms, which was brought to the attention of the committee by the Norfolk District Medical Society.

Dr. Hornor said that the committee had reviewed the report of the Committee Appointed to Confer with the Massachusetts Hospital Association and approved the recommendations contained in that report.

Dr. Hornor moved the adoption of the report as a whole. This motion was seconded by Dr. Cheever, and it was so ordered by vote of the Council.

*Subcommittee (of the Committee on Public Relations) to Meet with the Medical Advisory Committee of the Industrial Accident Board*—Dr. Daniel J. Ellison, Middlesex North, chairman.

This report (Appendix No. 8) was offered by Dr. Ellison. He said that, although his committee had been originally appointed to confer with the Medical Advisory Committee of the Industrial Accident Board, it had been directed by the Committee on Public Relations to take up directly with the board certain problems that had arisen.

He said that the first problem had to do with a complaint that certain insurers and employers were in fact compelling injured employees to submit to treatment at the hands of surgeons and at hospitals not of their own choice and that such employers even went so far as to discharge the injured workman if he did not acquiesce.

He added that Mrs. Tousant, chairman of the Industrial Accident Board, had informed him that if any doctor knows of such a case and will present all the facts in writing to her, including the date of the accident, the name of the employee and of the foreman, nurse or other person engaging in the illegal action, she will promptly put a stop to it. He pointed out that it must be obvious that the chairman of the board could not act on mere gossip.

The second problem had to do with a person who allegedly sustained a hernia in the course of his employment. The insurance company denied responsibility, and the injured workman privately contracted with a doctor of his own choice for the repair of the hernia. Under the contract the doctor charged the workman \$250, out of which amount the doctor agreed to and did pay the hospital bill. Subsequently, the Industrial Accident Board found that the insurance company was liable. The plaintiff then tried to recover the \$250 that he had expended. Dr. Ellison said that his committee agreed with Mrs. Tousant that the insurer should be liable only for the amount usually allowed by the board as compensation for the surgeon and hospital in an uncomplicated case of this kind.

Dr. Ellison said that the Industrial Accident Board was being greatly disturbed by a problem that was becoming widespread, especially in Boston. A workman is said by a physician to have sustained an industrial hernia. The workman is forthwith sent into some private hospital and operated on. No records or very sketchy records are kept. There is no proof that a herniotomy has been done. There

Dr. Richard Dutton, Middlesex East, asked whether, if the Approving Authority was now in effect, it applied to all candidates eligible for examination. Dr. Gallupe explained that those who entered a medical school after January 1, 1941, must graduate from an approved school. Otherwise, they are not permitted to take the examination leading to licensure in Massachusetts. In addition he pointed out that such graduates are not permitted to practice medicine anywhere in the United States. He said that the effective date of the present law was originally January 1, 1939, and that it was amended so as to give the substandard schools two years' additional grace. He pointed out that there was a bill before the Legislature that would further postpone the effective date of this law until three years after the close of the present war.

Dr. Paul J. Jakmauh, Norfolk, moved as an amendment to Dr. Browne's motion that the committee be instructed to ask leave to withdraw these bills and therefore give the committee further time to study and present the matter to us. This amendment was seconded by Dr. Merrill C. Sosman, Suffolk.

The President called for the vote on this amendment, but before it could be completed Dr. Browne moved that the matter be tabled. This motion was seconded by Dr. Leavitt.

Dr. Humphrey L. McCarthy, Norfolk, asked if, in the event that this motion prevailed, it would mean that the Council took no action on these bills. He was informed by the President that that was his conception of the situation. Dr. McCarthy pointed out that the Committee on Legislation voted unanimously to oppose these measures. He added that it was his belief that the chairman of that committee should not instigate their being tabled.

At that point Dr. Leavitt suggested that Dr. Browne withdraw his amendment saying that he, Dr. Leavitt, would make the same amendment on Dr. Browne's withdrawal. He expressed the thought that this might be a more seemly way to present this type of motion to the Council.

Dr. Browne did not acquiesce. He thought that there was merit in not having the Council go on record as opposed to matters that it might deem wise to favor in the future.

At that point the President said, as a means of clearing the air, that he would entertain a motion of support for the Committee on Legislation. Dr. Schadt so moved. This motion was seconded by Dr. Leavitt, and it was so ordered by vote of the Council.

Dr. Browne next referred to a bill introduced by a chiropodist, which would permit chiropodists to use a hypodermic syringe in the course of their professional activities. He said that his committee had opposed this bill and that it had been withdrawn after a hearing before the Committee on Public Health of the Legislature.

Dr. Browne next grouped several bills that would

further postpone the operative date of the Approving Authority. These bills would, he added, delay the operative date from one to three years after the termination of the present war. He said that the committee opposed the bills.

Dr. Browne next referred to a bill that would create a State University Medical School.

Dr. Browne spoke of a plan to form a committee of fifty-four to be made up of the president and two others from each district society. He said that this plan included the thought that eighteen of this number might wait on the Governor in case any of the bills, referred to as being opposed by the committee, should get to him for his signature, and explain why he should not sign them.

Dr. Browne expressed his thanks for the help that he had been given by Dr. Charles E. Mongan. He also spoke of the importance of having our members present at the hearings on these bills. He quoted a member of the Committee on Public Health as saying that the objectionable bills had a 50 per cent chance of going through.

He referred to the so-called "Chiropractic Bill" and said that, in this connection, the committee stood for one single standard, which all should meet if they would practice the healing art.

Dr. Browne moved that the Council extend its thanks to Dr. Brainard F. Conley, former chairman of the Committee on Legislation, for the years he had effectively put into the legislative work. This motion was seconded by Dr. Walter H. Pulsifer, Plymouth, and it was so ordered by vote of the Council.

Dr. Browne moved the adoption of the report. This motion was seconded by Dr. Pulsifer, and it was so ordered by vote of the Council.

Dr. Browne said he made this motion subject to amending the report when it appeared in formal shape.

The Council adjourned at 2:00 p.m. for luncheon and reconvened at 2:45 p.m.

*Committee on Public Relations*—Dr. Albert A. Hornor, Suffolk, secretary.

This report (Appendix No. 7) was offered by Dr. Hornor.

In offering this report, Dr. Hornor said that the Committee on Public Relations had considered the question of policy to be followed in supplying advice to lay inquiries coming into a community about the selection of a family physician. He said that it was the opinion of the committee that all requests for information of this kind should be referred to the secretary of the respective district society.

He offered four recommendations, all of which he said had been approved by the Committee on Public Relations. The first was as follows:

In view of the probability of not getting an ideal man now, the Society should not try to hire a publicity agent at the present time.

hospital, as well as surgery and obstetrics. And I am sure that if we can move on that basis it will be a much healthier approach than what has occurred in some other sections.

I think that it should be drawn to your attention that in California, where they have only approached our present figures, or a little bit more, in a five-year period, and where they have not had the healthy relation of general goodwill that Massachusetts has experienced, the profession seems to be taking a definite step in co-operation with the governor to institute a program of compulsory health insurance. It behooves us to prove that a voluntary program can succeed, because if not, this may lead to a feeling on the part of the profession that no ultimate solution can be achieved other than compulsory health insurance.

The revision of the fee schedule by the specialists' group is progressing. Of course, it must be slow and should be accurate. Many men have given a good deal of time and thought to establishing a more adequate schedule, and it is my hope that after each group has completed its part, at least the chairman of each group will evaluate the conception of the value of the service of other groups in contrast with his own personal conception of the value of his own service. That certainly is a fair approach to the problem of getting an equitable base of compensation through all the groups.

There has been a change in the Board of Directors, owing to the untimely loss of the services of Dr. J. Harper Blaisdell. His place has been filled by Dr. Norman Welch, which gives representation in the Board of Directors of an internist, which means, of course, that if within this year we can move effectively in the problem of arranging for some medical care in the hospital his presence will contribute a great deal.

I think that we should think in terms of stabilizing our program. We have sought to eliminate problems and frictions and misunderstanding. There are, of course, innumerable "bugs," as in any new venture, that must be ironed out. The fee schedule is one on which we are putting a great deal of time. We have achieved a great deal more satisfactory contact with groups, so far as publicity is concerned, since we have the full-time services of Mr. Cunningham. He is trying to approach hospital staffs and to discuss the problems with them, and I hope that he will be given a welcome reception. He is also trying to interest other groups. Publicity is difficult. We do have plans, as you have noted, to get periodic records and statements into the *New England Journal of Medicine*. Beyond that it is difficult. The hired layman can contribute some time to this aspect, but, those of us who are serving you in trying to make this program roll are limited in our time, and we cannot indulge in much writing on the side regarding the meetings that we have to keep this thing going.

It should be kept in mind that there are channels through which you can move with reference to the corporation that you have established. Physicians have an effective control over this organization through the Executive Committee of the Society, the members of which, as you know, constitute the voting members of the corporation and are in contact with physicians all over the Commonwealth and sensitive to their opinions. The voting members at all times are free to send recommendations and memoranda to the Board of Directors, which, of course, would be seriously weighed. On any major departures in reorganization and extensions, as you remember, under the factors we call vital medical matters, the board is required to give thirty days' notification to the voting members, the Executive Committee, so that any radical action can be immediately held up until further consideration is given to it.

All in all, things seem to point to the fact that this year will prove that we have initiated a successful venture. I surely hope so.

Dr. McCann left the platform amid applause.

#### REPORTS OF SPECIAL COMMITTEES

*Committee on Cancer* — Dr. George A. Moore, Plymouth, chairman.

No report.

*War Participation Committee* — Dr. Guy L. Richardson, Essex North, chairman.

This report, which is as follows, was presented by Dr. Richardson:

The situation in Massachusetts regarding doctors' certificates for change of employment appears to be satisfactory to the War Manpower Commission. Thus far we have not been asked to review any of these certificates. In a letter to me under date of January 13, 1945, Mr. James G. Walsh, assistant state director, writes: "We would very much welcome your continued assistance to the War Manpower Commission throughout the Commonwealth and I wish to assure you that the announcement by this commission that medical certificates would be reviewed by your committee has been very helpful." At the present time there is no outstanding case which this office feels should be sent to you for review. In general, the doctors have co-operated exceedingly well. Again, let me thank you for your continued co-operation in this matter."

The Office of Price Administration has several times called on us for assistance. We have appointed local war participation committees to assist the ration boards in communities where there was need for such help. In some cities, physicians' committees to do this work had already been in operation and were of distinct benefit to the rationing plan.

Miss Elizabeth Golden, rationing specialist of the Office of Price Administration, makes the following statement: "Throughout the State the result of establishing these committees has been to reduce immediately the number of spurious requests for extra foods. Now that it is generally known that competent medical authorities are controlling the rations, doctors who heretofore have signed with little regard for what they are asking are more inclined to be careful and frequently deny requests for special indulgence." These committees are guided by the general directions on food rationing from the Medical Advisory Committee, under the chairmanship of Dr. Joseph Garland.

Doctors' prescriptions for heavy cream have steadily lessened. The War Food Administration now receives two or three a day instead of the one hundred a day formerly received. Only thirty-five of these prescriptions have been approved since August 1, 1944. Cream is not a rationed product, but the need to conserve fats is great. The publicity given by us in this matter has helped. Dr. Garland and his committee have done the real job.

In our October report to the Council we told you that we were gathering data on the adequacy of hospital care for emergency cases. In the main the response from the hospitals was excellent. One or two did not reply, and the replies from a few did not contain the information desired. To summarize the results: no problem in this respect appeared to exist in the Springfield and Worcester hospitals, all answering that no emergency patients were refused admission. These answers placed Springfield and Worcester with the smaller cities and towns, which were considered by us not to need this inquiry. The problem was thus narrowed to Boston. More than two thirds of the Boston hospitals admitted having to refuse admission to some or many emergency cases because of lack of personnel or beds.

On January 17, at our request, we held a joint meeting with the Committee Appointed to Confer with the Massachusetts Hospital Association, of which Dr. Walter Phippen is chairman. Ways and means to lessen the frequency of the refusal of emergency cases were considered. It was decided to seek further co-operation from physicians in agreeing to postpone admission of an elective case to allow admission of another physician's emergency case, to discriminate more carefully in labeling a case as an emergency (some hospitals have a committee of doctors to check the question of urgency) and to discharge patients from the hospital as early as possible.

It was voted to recommend to the Council that the Committee Appointed to Confer with the Massachusetts Hospital Association inform that association that we as physicians are fully cognizant of the immensity of their problem in these war years and that we believe they have fulfilled their obligations well, and further that we welcome





tract all those things for which the hospital usually made a charge. He added that this left the matter squarely in the hands of the radiologist to make whatever arrangements he and the hospital could jointly agree on.

Dr. Hornor said that there evidently was a disposition on the part of radiologists to change certain practices that had grown up in this specialty and that in this spirit they had approached the Committee on Public Relations last summer so that they might have the help of the Massachusetts Medical Society in this purpose. He added that the Society should give them all the help it could.

Dr. John Fallon, Worcester, expressed the view that the matter should be further considered by the radiologists and the committee. He added that the inclusion of x-rays in the Blue Cross contract should not defer the Society from pursuing this subject further.

Dr. Bagnall said that the x-ray group had demonstrated and exercised more constructive thinking in the last year than it had in all the time that has elapsed since the start of the Blue Cross. He said that, in view of this fact, he believed the group should have been given more time. He added that he voted against the inclusion of x-ray in the contract when this matter was recently before the directors of the Blue Cross.

Dr. Howard F. Root, Suffolk, asked if, in the discussions on this subject, any consideration had been given to the possibility of separating the hospital from the professional costs. Dr. Bagnall said that Dr. Faxon could answer the question better than he.

Dr. Dameshek moved as an amendment the adoption of the recommendation of the Executive Committee.

Dr. Phippen was asked by the President if he would accept the amendment. He said that he was a little disposed not to accept the amendment. He believed the report should be voted on as presented. In support of this report he said that apparently brevity is not always conducive to clarity. The report as modified, he thought, was fairly clear. He added that what the committee intended to say in the second paragraph, the matter discussed by Dr. Faxon, was that a hospital should not exploit its x-ray department. He said that no one could question the fact that the radiologist furnishes medical service and that from the standpoint of this report nothing was said whether the Blue Shield or the Blue Cross should make provisions for x-ray. What the committee did say, he continued, was that, if either of them was going to take over the full professional service of the radiologist, the Blue Shield was the logical one to do it.

Dr. Faxon agreed with the President that the radiologist had begun to show a little constructive

thinking in the matter during the last year. He expressed the opinion that the problem could be solved by the hospitals and radiologists getting together on it.

Dr. Leavitt reiterated his belief that there seemed to be some sort of argument going on among the members of the x-ray society and that the latter should settle their own differences.

The amendment to refer this matter back to the committee for clarification was put and was lost.

The original motion was put by the chair, and so ordered by vote of the Council.

*Committee on Postwar Planning* — Dr. Howard F. Root, Suffolk, chairman.

This report (Appendix No. 9) was offered by the chairman. He said that Dr. Leroy Parkins had agreed to serve as secretary.

He announced that the committee had organized many subcommittees of the whole. These had to do with hospitals, postgraduate education, medical schools, Massachusetts Medical Society organization and medical economics.

The report quoted from the record of the Council meeting held on June 9, 1936, regarding approved recommendations for the establishment of local medical-service councils. Dr. Root said that twenty-three local health councils now exist and co-operate with the Massachusetts Central Health Council. He added that physicians should take more interest in them for the purpose of their greater activation and that additional councils should be organized. Dr. Root moved acceptance of this part of the report. This motion was seconded by Dr. Phippen, and it was so ordered by vote of the Council.

Dr. Root moved that the Council authorize the President to inform the president and secretary of each district society, the chairman of each health council, the superintendent or chairman of the staff and the chairman of the board of trustees of each hospital in the Commonwealth whose staff members are in community practice concerning the following resolution:

RESOLVED, That the Council of the Massachusetts Medical Society, having in mind the unusual problems of medical care to be presented now and in the postwar period, recommends (1) the formation of health councils where none exist, or when the present council is inactive, to be composed of physicians and dentists, hospital trustees, public-health specialists, educators, editors, employers and representatives of labor and groups concerned with the distribution of medical care, to consider and adopt further measures for extending medical services in the community and increasing preventive-health education both by local effort and through co-operation with state and federal bodies; (2) more active participation by physicians in the work of health councils already in active existence; and (3) that the Committee on Public Relations implement these recommendations in such manner as the committee deems most profitable.

This motion was seconded by Dr. Ohler, and it was so ordered by vote of the Council.



suggestions for added co-operation by the medical profession to the end that a real emergency be not refused admission.

Dr. Richardson moved the acceptance of the report and the adoption of the recommendation contained therein. This motion was seconded by Dr. Phippen, and it was so ordered by vote of the Council.

*Committee on Rehabilitation*—Dr. Joseph H. Shortell, Suffolk, chairman.

No response.

*Committee Appointed to Confer with the Massachusetts Hospital Association*—Dr. Walter G. Phippen, Essex South, chairman.

Dr. Phippen in reading the following report said it was somewhat different from that submitted to the Executive Committee and set forth in the pamphlet of advance information.

The Committee Appointed to Confer with the Massachusetts Hospital Association was invited to meet with representatives of the New England Roentgen-Ray Society and the Section of Radiology of the Massachusetts Medical Society on November 13, 1944. Those present at the meeting were Dr. Hugh F. Hare and Dr. George Levene, of the New England Roentgen-Ray Society, Dr. George Holmes, of the Massachusetts General Hospital, Dr. Merrill C. Sosman, of the Peter Bent Brigham Hospital, Dr. Stanley Wilson, of the Salem Hospital, and the committee (Dr. Walter G. Phippen, chairman, Dr. Elmer S. Bagnall, Dr. Edwin D. Gardner, Dr. John Fallon and Dr. Frederic Hagler).

A long and friendly discussion of the whole situation of the relation of the radiologist to the hospital and to the Blue Cross and Blue Shield ensued. The members of the committee thought that they could unanimously agree to the resolutions drawn up by the New England Roentgen-Ray Society and the Section of Radiology, and unanimously adopted by them on November 3, 1944, as follows:

The professional status of the radiologist in a hospital should be comparable to the status of other chiefs-of-service in that hospital.

It should be agreed that a hospital should not make excess profit from medical services. It is agreed that a hospital with the overhead necessary to maintain a medical service at a high standard should be reimbursed for the actual expenses of maintaining a department, with a fair share of overhead, investment of capital, maintenance and replacement of equipment.

If the Massachusetts Hospital Association agrees to these basic principles, fees can be reduced and the cost of medical care can be lowered.

The committee members were also of the opinion that the radiologist furnished medical service rather than hospital service and that therefore payment for his service should logically come under the Blue Shield rather than under the Blue Cross.

The committee was unanimous in voting to present this statement to the Executive Committee at its next meeting in the hope that it could support this resolution and present it to the Council for its approval.

Dr. Phippen moved the adoption of the report and the adoption of the resolution. This motion was seconded by Dr. Hornor.

Dr. Nathaniel W. Faxon, Suffolk, asked that the recommendation of the Executive Committee in connection with the matter be read. Dr. Leavitt read the recommendation as follows:

The Executive Committee recommends that this report be referred back to the committee for clarification.

Dr. Faxon said in general he was in accord with the report. He thought, however, as it referred to the profit made by hospitals, the word "undue" should be made to appear before the word profit. Speaking for one hospital, he said that he subscribed to the feeling that a great many radiologists have, namely, that hospitals should not make a large profit out of their profession and practice. He added that some hospitals will probably not subscribe to this view. He said that he also believed that members of hospital staffs should not profit unduly by the fact that they are members of such staffs.

Dr. Leavitt, in expressing the views of the Executive Committee in connection with this report, said that the committee was very much in the dark about what was actually going on. He added that the whole thing sounded as if there was an argument somewhere and that the committee thought that it should know more about the matter before it lent itself to the argument.

Dr. William A. R. Chapin, Hampden, expressed support for the Executive Committee's recommendation.

In confirmation of the point made by Dr. Leavitt, that there seemed to be an argument going on somewhere, he said he had talked with Dr. Jackson, whom he identified as "our radiologist at home," and that the latter said that he had attended the meeting of the radiologists at which these principles were adopted and that the arguments for and against were so mixed up that he, Dr. Jackson, could not make sense out of them.

Dr. Reardon asked if Dr. McCann could give the Council any information as to what was the practice with regard to x-rays in other state medical-service plans. Dr. McCann replied that in those plans that included x-rays a cash allowance was made, in most cases up to \$15.00. He added that the New Jersey plan did not include x-ray.

Dr. Faxon said that a substantial number of Blue Cross plans include x-ray as part of what is spoken of as hospital expense. He added that the Massachusetts Blue Cross was disposed to treat the radiologists as fair as possible and that this problem had been debated ever since Blue Cross started and was continuing to be debated at the present time. He finally said that he himself had not arrived at the answer.

Dr. Hornor pointed out that, so far as the inclusion of x-ray in the Massachusetts Blue Cross plan is concerned, it was an accomplished fact. Dr. Faxon said that although this was so it was with reluctance that such a policy had been established. He added that the Blue Cross had been trying to get this matter settled for three or four years and was not getting anywhere. He also said that, at the last meeting of the Blue Cross directors, the majority felt that it was the only thing to do.

Dr. Bagnall said that what the Blue Cross directors actually voted to do was to include in the con-

It was pointed out that the United States Public Health Service expects to get money to finance stated services in their hospital situations.

Former Governor Saltonstall has passed on to Governor Tobin the appointment of the committee which would be expected to study the whole situation, especially the ability of nonteaching hospitals to set up residencies.

The American Hospital Association is also devising a questionnaire to be sent to hospitals for a survey, conducted under Dr. Bachmeyer, with Dr. Norby as assistant director.

It is possible that the Army and Navy will take over refresher courses, so-called, and carry them on in Army, Navy or Veteran hospitals. Additional Veteran hospitals might well be built close to medical centers instead of in the country, as in prewar times.

It was pointed out that it was necessary to sort out these war medical graduates and select those worth teaching and not waste time on the others.

Lastly, it was suggested that an extern service might serve to take care of a great many of these returning veterans.

Dr. Faxon moved the acceptance of the report. This motion was seconded by Dr. Ober, and it was so ordered by vote of the Council.

*Committee on Medical Information Bureau* — Dr. Walter G. Phippen, Essex South, chairman.

This report, which was offered by Dr. Phippen, is as follows:

Since the last meeting of the Council, the Bureau of Clinical Information of the Massachusetts Medical Society has become a going concern. Invitations were sent to twenty-two hospitals in Greater Boston to meet with this committee on October 25, 1944. Twenty hospitals accepted and sent a representative to the meeting. All not only were co-operative and offered the co-operation of their hospitals but were enthusiastic about the project. The Bureau opened on November 13, 1944, with Miss Mary D. Gaston in charge as secretary. An announcement of this fact was sent out as follows: to the secretaries of every district medical society, with the request that it be read at the next meeting; to the secretaries of every state medical society in the United States; to the secretary of the American Medical Association; to the editors of every state medical journal, with the request that they print it; to the 240 hospitals in Massachusetts, with the request that they post it; to the editor of the *Journal of the American Medical Association*, with the request that he print it; to every Army (76) and Navy (20) hospital in Massachusetts, with the request that they post it; and to every member of the Massachusetts Medical Society with his bill for dues.

Seven hospitals sent us enough material concerning non-operative clinics, conferences, special rounds and so forth so that we could publish our first bulletin on November 20. This went to all the co-operating hospitals. By December 5, we had many requests for the bulletin and eleven hospitals had contributed material so that we issued a second bulletin, sending it to all the contributing hospitals and all who had requested it.

It was originally intended to issue the bulletins either every three or six months, but we found that most of the hospitals change their schedules every month. It was decided that we should issue the bulletin every month, and consequently the third number was sent out on January 2. It has proved to be very much desired, and we have had so many requests from physicians, hospitals, the Army, the Navy and many others, that the February mailing list will probably reach 180.

We have had many interesting letters from various parts of the Commonwealth. A particularly enthusiastic one came from Cape Cod, applauding the Bureau and asking for the bulletin. The Dispensary of the First Service Command also asked to be placed on the mailing list. Altogether we are much pleased with the reception accorded the bulletin.

In all, twenty-one hospitals and the Lahey Clinic now send us both operating lists and material for the bulletin. The demand for information concerning operations has not been so great as was expected, to date only about 75 such requests having been received. Contrary to expectations, most requests come between 11 a.m. and 5 p.m. Only one request came before 9 a.m., and only 2 after 5 p.m. It may be necessary to adjust our office hours.

The Bureau hopes to be of still greater usefulness in the future when it becomes better known. Particularly it anticipates a much broader usefulness when plans are perfected for postgraduate teaching for returning service men. It is anxious to co-operate with the national, state and local committees on postwar planning and stands ready to tabulate any information concerning internships, residencies and courses, and have it currently available for enquiring servicemen.

The committee begs your indulgence to continue on until the annual meeting.

Dr. Phippen moved the adoption of the report. This motion was seconded by Dr. Ober, and it was so ordered by vote of the Council.

*Postwar Loan Fund Committee* — Dr. George Leonard Schadt, Hampden, chairman.

This report (Appendix No. 10) was offered by Dr. Schadt who referred to the results of the questionnaire that had been sent to the members of the Society. Dr. Schadt made use of certain slides to illustrate the information gathered in this manner. He said that the questionnaire had been sent to 4600 fellows; 1916, or 41.6 per cent, had responded as of January 24, 1945. He added that this was an excellent return: 14 to 20 per cent being considered good. He said that 1484 members of the Society approved of the plan, that 380 disapproved and that there were 66 blanks. He said that the committee was inclined to look on this as a mandate to go through with the plan.

He said that there were three districts that showed disapproval — Bristol North, Franklin and Worcester North.

He pointed out that the report that was before the Council differed somewhat from that submitted in April, 1944; that this was principally by way of certain additions that had come about as the result of an analysis of the questionnaire by the committee.

At that point Dr. Schadt read the report in its entirety and the recommendations contained therein. He moved its acceptance. This motion was seconded by Dr. Richardson, and it was so ordered by vote of the Council.

Dr. Schadt moved the adoption of the first recommendation. This recommendation is as follows:

The Postwar Loan Fund Committee recommends that the Council of the Massachusetts Medical Society authorize the establishment of a postwar loan fund.

This motion was seconded by Dr. Chapin.

Dr. Parkins said that, while he was much in favor of helping people, he wondered if this was the way to go about it. He placed \$30,000 as the amount that would be raised under this plan. He thought this would be entirely inadequate. He expressed the thought that the money raised could be put

*Subcommittee (of Committee on Postwar Planning)  
on Postgraduate Education — Dr. W. Richard  
Ohler, Norfolk, chairman.*

This report, which is as follows, was offered by the chairman:

As a result of conferences with various people interested in the problem of postgraduate medical instruction and with full realization of the importance of the problem in this period, the Subcommittee on Postgraduate Education submits these objectives.

First, that this committee co-operate in every way possible with the subcommittees on hospitals and medical schools in the work of providing residencies or other opportunities for further hospital experience or instruction for returning doctors.

Second, that this committee gather information concerning opportunities for postgraduate work in Massachusetts and elsewhere in the country.

Third, that, in co-operation with the subcommittees on hospitals and medical schools, this committee provide or assist in providing a program of postgraduate refresher courses to be given both in Boston and in other parts of the Commonwealth for returning doctors and other interested physicians. That in so doing, this committee also co-operate with schools of public health, organized teaching clinics, the State Department of Public Health and other scientific state and federal agencies.

In order that progress be made as quickly as possible and with as little confusion as possible Dr. Ohler offered the following motion:

That the Council authorize the Subcommittee on Postgraduate Education to make available information regarding all opportunities for postgraduate medical instruction in co-operation with the Bureau of Clinical Information, and to institute a program for the extension of postgraduate medical instruction in the entire state, and, in so doing, to seek the co-operation of approved medical schools, schools of public health, teaching clinics, the State Department of Public Health and other state and federal agencies.

This motion was seconded by Dr. Schadt and it was so ordered by vote of the Council.

*Subcommittee (of Committee on Postwar Planning)  
on Medical Schools — Dr. Charles F. Branch,  
Suffolk, chairman.*

The report, which is as follows, was offered by Dr. Branch:

This committee has a preliminary report in which it would like to make some general observations on the part that medical schools may play in the planning of postwar courses, and would also like to offer a resolution that it believes is pertinent to postwar medical education in this state.

Under the heading of general observations we wish to point out that there are three general types of postgraduate opportunity that should be freely available for doctors returning from military service: resident training, which is entirely carried on in hospitals and is essentially a hospital problem, but in which the profession at large and the medical schools take part; fellowship opportunities for those wishing to qualify for teaching and investigative work in the preclinical sciences, which will be found largely in the medical schools; and refresher-type courses for those who have been recently graduated and may feel that they have been "short-changed" in their regular medical education.

In all these types of training the medical schools are anxious to participate as their resources permit, and are already making plans for such participation. It is pertinent to add, however, that the medical schools are still overloaded with their wartime commitments and cannot be expected to assume large new burdens of this sort until there is a substantial return of the teachers now on leave.

The matter to which we have addressed our resolution is one on which immediate action seems needed, else it be too late, and our returning fellows will face a profession which will continue to be annually diluted and weakened by graduates of unapproved medical schools.

WHEREAS, The standards of medical education in Massachusetts have been notoriously low for a long period of time, and

WHEREAS, A law providing for their improvement through the creation of an approving authority was placed on the statute books in 1936, and was amended in 1939, such amendment having been made in the interest of those upon whom the law was thought to work some hardship, and

WHEREAS, This amended law is now in operation and is presumably capable of elevating the educational standards of the Commonwealth; therefore be it

RESOLVED, That, in the interest of public health and the standards of medical education and medical practice, it is vitally important that the Massachusetts Medical Society immediately take an active part in maintaining and supporting the law as it now stands.

Dr. Leroy E. Parkins, Suffolk, moved the adoption of the resolution. This motion was seconded by Dr. Phippen, and it was so ordered by vote of the Council.

*Subcommittee (of Committee on Postwar Planning)  
on Hospitals — Dr. Nathaniel W. Faxon, Suffolk, chairman. Dr. Faxon offered the following  
as a report of progress:*

Postwar planning for doctors in hospitals divides itself into two parts: residencies lasting one or more years within the hospital and courses, which may or may not be held within the hospital, lasting from three to six months. The latter may be carried on in hospitals or medical schools. Certain points seem to be very definite: only veterans shall be considered in this and, so far as residents are concerned, hospitals must control the selection.

Residencies can be increased in present hospitals or can be established in hospitals which do not now have them. As an example, the Massachusetts General Hospital originally had 85 on the resident staff; it now has 64. They probably can be increased to about 100, with 60 recent medical-school graduates, as at present, and 40 returning veterans. There is no doubt that other teaching hospitals could provide a similar increase. Hospitals such as the Cambridge, Newton, Salem, St. Luke's in New Bedford, Worcester City and the Springfield, could undoubtedly develop real residencies, especially if some members of the staff could be induced to talk over the matter seriously. Other smaller hospitals might not be able to do this because of the staff's not really being competent to undertake such leadership. This will have to be explored.

Dr. Miller, of the American College of Surgeons, is examining the possibility of having teaching hospitals take returning veterans for from six months to one year as residents, with the understanding that they should be then moved to nonteaching hospitals where they would continue to serve as residents for another year.

Dr. A. J. Hockett, of the King County Hospital System, Seattle, Washington, has suggested a training program whereby a man after spending a certain time in the hospital would be apprenticed to members of the hospital staff to serve as an assistant during the remainder of his service. Graham Davis, of the Kellogg Foundation, is working on this in Michigan.

It was thought that hospitals would probably want to go back to approximately their prewar plans, with internships and residencies on a twelve months' basis and in hospitals such as the Massachusetts General four to five years in medicine and surgery; that the returned veteran residency should be additional to the present one; that perhaps certain veterans could be set up as instructors, either with a slight polishing course or even without it, as for instance, Richard Thompson in Salem, Pilcher in Newton, Carmody in Worcester and so forth.

It was pointed out that the United States Public Health Service expects to get money to finance stated services in their hospital situations.

Former Governor Saltonstall has passed on to Governor Tobin the appointment of the committee which would be expected to study the whole situation, especially the ability of nonteaching hospitals to set up residencies.

The American Hospital Association is also devising a questionnaire to be sent to hospitals for a survey, conducted under Dr. Bachmeyer, with Dr. Norby as assistant director.

It is possible that the Army and Navy will take over refresher courses, so-called, and carry them on in Army, Navy or Veteran hospitals. Additional Veteran hospitals might well be built close to medical centers instead of in the country, as in prewar times.

It was pointed out that it was necessary to sort out these war medical graduates and select those worth teaching and not waste time on the others.

Lastly, it was suggested that an extern service might serve to take care of a great many of these returning veterans.

Dr. Faxon moved the acceptance of the report. This motion was seconded by Dr. Ober, and it was so ordered by vote of the Council.

*Committee on Medical Information Bureau* — Dr. Walter G. Phippen, Essex South, chairman.

This report, which was offered by Dr. Phippen, is as follows:

Since the last meeting of the Council, the Bureau of Clinical Information of the Massachusetts Medical Society has become a going concern. Invitations were sent to twenty-two hospitals in Greater Boston to meet with this committee on October 25, 1944. Twenty hospitals accepted and sent a representative to the meeting. All not only were co-operative and offered the co-operation of their hospitals but were enthusiastic about the project.

The Bureau opened on November 13, 1944, with Miss Mary D. Gaston in charge as secretary. An announcement of this fact was sent out as follows: to the secretaries of every district medical society, with the request that it be read at the next meeting; to the secretaries of every state medical society in the United States; to the secretary of the American Medical Association; to the editors of every state medical journal, with the request that they print it; to the 240 hospitals in Massachusetts, with the request that they post it; to the editor of the *Journal of the American Medical Association*, with the request that he print it; to every Army (76) and Navy (20) hospital in Massachusetts, with the request that they post it; and to every member of the Massachusetts Medical Society with his bill for dues.

Seven hospitals sent us enough material concerning non-operative clinics, conferences, special rounds and so forth so that we could publish our first bulletin on November 20. This went to all the co-operating hospitals. By December 5, we had many requests for the bulletin and eleven hospitals had contributed material so that we issued a second bulletin, sending it to all the contributing hospitals and all who had requested it.

It was originally intended to issue the bulletins either every three or six months, but we found that most of the hospitals change their schedules every month. It was decided that we should issue the bulletin every month, and consequently the third number was sent out on January 2. It has proved to be very much desired, and we have had so many requests from physicians, hospitals, the Army, the Navy and many others, that the February mailing list will probably reach 180.

We have had many interesting letters from various parts of the Commonwealth. A particularly enthusiastic one came from Cape Cod, applauding the Bureau and asking for the bulletin. The Dispensary of the First Service Command also asked to be placed on the mailing list. Altogether we are much pleased with the reception accorded the bulletin.

In all, twenty-one hospitals and the Lahey Clinic now send us both operating lists and material for the bulletin. The demand for information concerning operations has not been so great as was expected, to date only about 75 such requests having been received. Contrary to expectations, most requests come between 11 a.m. and 5 p.m. Only one request came before 9 a.m., and only 2 after 5 p.m. It may be necessary to adjust our office hours.

The Bureau hopes to be of still greater usefulness in the future when it becomes better known. Particularly it anticipates a much broader usefulness when plans are perfected for postgraduate teaching for returning service men. It is anxious to co-operate with the national, state and local committees on postwar planning and stands ready to tabulate any information concerning internships, residencies and courses, and have it currently available for enquiring servicemen.

The committee begs your indulgence to continue on until the annual meeting.

Dr. Phippen moved the adoption of the report. This motion was seconded by Dr. Ober, and it was so ordered by vote of the Council.

*Postwar Loan Fund Committee* — Dr. George Leonard Schadt, Hampden, chairman.

This report (Appendix No. 10) was offered by Dr. Schadt who referred to the results of the questionnaire that had been sent to the members of the Society. Dr. Schadt made use of certain slides to illustrate the information gathered in this manner. He said that the questionnaire had been sent to 4600 fellows; 1916, or 41.6 per cent, had responded as of January 24, 1945. He added that this was an excellent return: 14 to 20 per cent being considered good. He said that 1484 members of the Society approved of the plan, that 380 disapproved and that there were 66 blanks. He said that the committee was inclined to look on this as a mandate to go through with the plan.

He said that there were three districts that showed disapproval — Bristol North, Franklin and Worcester North.

He pointed out that the report that was before the Council differed somewhat from that submitted in April, 1944; that this was principally by way of certain additions that had come about as the result of an analysis of the questionnaire by the committee.

At that point Dr. Schadt read the report in its entirety and the recommendations contained therein. He moved its acceptance. This motion was seconded by Dr. Richardson, and it was so ordered by vote of the Council.

Dr. Schadt moved the adoption of the first recommendation. This recommendation is as follows:

The Postwar Loan Fund Committee recommends that the Council of the Massachusetts Medical Society authorize the establishment of a postwar loan fund.

This motion was seconded by Dr. Chapin.

Dr. Parkins said that, while he was much in favor of helping people, he wondered if this was the way to go about it. He placed \$30,000 as the amount that would be raised under this plan. He thought this would be entirely inadequate. He expressed the thought that the money raised could be put

to better use if it were used as a credit pool against which a much larger sum could be made available through regular borrowing channels. He thought that the benefits under this plan should not be limited to those who were members of the Massachusetts Medical Society at the time of their enlistment, in other words, that the list should include those who were eligible for such membership.

Dr. Chapin took sharp issue with the previous speaker and urged the Council to try out the plan as outlined for one year.

Dr. Faxon said that he believed that the last recommendation in the list of recommendations read by Dr. Schadt would set up a permanent loan fund. He added there was some serious question in his mind whether this was a thing the Society should do. He said that this recommendation should contain some provision whereby the fund might be used for other than its original purpose when that particular purpose no longer existed.

Dr. Schadt could not agree with Dr. Parkins on the amount of money which the latter thought would be raised by the plan that the committee proposed. Dr. Schadt said that the amount would be at least \$45,000. He referred to the G. I. Bill of Rights and pointed out that it was possible under this legislation for the veteran to borrow up to \$4000 but that the Government guarantees but \$2000 of this amount and if the veteran wants the additional \$2000 he must have collateral. He added that the one objective of this fund was to make immediately available financial assistance to those of the members who, having served in the present war, are in need of such assistance at the time of their separation from the armed forces.

Dr. Schadt said he did not know and had no way of determining the number who would apply for a loan under this proposed plan.

He said that, although it was not planned to send the questionnaire to those in the service, certain replies had been received from servicemen. He said that certain of these indicated a need for such a fund.

Dr. Connor was critical of the way in which the questionnaire had been handled. He thought it should have been conducted as an Australian ballot is usually conducted. He expressed the view that the proposed fund was unnecessary because the serviceman's needs will be adequately cared for by the G. I. Bill of Rights. He said that, after the last war, he was able to negotiate a thousand-dollar loan without collateral. He added, "If the Massachusetts Medical Society feels so charitable about this matter, let us take the money we already have and place it behind the credit of any member who feels he may need a loan."

Dr. Parkins expressed the thought that the boys who will need help most are those who are not members of the Society.

Dr. Schadt said he was in agreement with Dr.

Parkins in this respect and that he personally thought that the proposed fund should be made available to every doctor in Massachusetts. He added that the committee was opposed to this all-inclusive feature. He said that the questionnaire indicated that only 52 of those who disapproved thought that the G. I. Bill of Rights would take care of the situation.

In answer to the criticism that the questionnaire was not conducted along the lines of an Australian ballot, he said that he questioned that anybody connected with the questionnaire remembered the names of those who recorded themselves in opposition. He added that 34 of those who approved and 3 of those who opposed made inquiries about the final disposition of the fund.

Dr. Carl Bearse, Norfolk, asked for how long a period of time, after being separated from the service, the veteran would be eligible to borrow from this fund.

Dr. Schadt answered this by saying that he thought that, inasmuch as this was for the immediate need of the returned doctor, it would probably end five years after the close of the war. He added that this was a detail that might be left to the board appointed to administer the fund and that once such details were established, the Executive Committee and the Council could pass on them at a later time.

Dr. Connor asked Dr. Schadt the following question: "Did you say that the G. I. Bill of Rights will not take care of the returning soldier doctor?"

Dr. Schadt replied that he had not said that. He added, however, that obtaining a loan under the G. I. Bill was a slow process, taking for consummation as much as seven weeks after the application was made.

Dr. Cheever said that he wanted to do everything possible for the returning veteran. He expressed the view that, although it seems that the Government is going to be very liberal with the veteran, no one actually knows just how liberal that aid is going to be. He said that the Society had the equivalent of something like \$200,000 in negotiable securities that it was at perfect liberty to use as loans. Why not, he asked, put this money out as loans to our members at 2 per cent interest? After the veterans have returned, he continued, the Society can evaluate the situation again and determine whether it wishes to go farther and to establish a separate loan fund. He thought that it was a mistake to designate definitely the final disposition of a fund. He concluded that this thing could be left in abeyance for the present without expressed approval of the report as a whole. He thought that the affirmation of a simple statement of the intention to help the veteran when, as and if such help was necessary was as far as the Society should go at present.

Dr. Schadt at that point was asked to read the recommendation before the Council. This he did as follows:

The Committee on Postwar Loan Fund recommends that the Council of the Massachusetts Medical Society authorize the establishment of a Postwar Loan Fund.

Dr. Cheever moved to amend the recommendation by adding to it the words "when, as and if necessary." This amendment was seconded by Dr. Richardson, who said that the adoption of this amendment would obviate the necessity of doubling the dues of members.

Dr. Fallon pointed out that it was obvious that everyone was in favor of some form of help for the returning serviceman whether it be by the G. I. Bill or by action of the Society. The Society had, however, he continued, a matured plan that had been considered by the committee for a long time. He expressed the thought that the Society could start out with this matured plan, collect the \$10.00 which could be spared this year, consider the suggestions that had been offered and possibly change the plan later so as to incorporate them.

Dr. Schadt took issue with Dr. Richardson's remarks to the effect that the plan proposed by the committee would double the dues of members. He said that the plan called for a specific assessment of \$10.00 for one year only. He added that whether or not there would be additional assessments depended entirely on separate action by the Council. He said that it was his frank opinion that if the Society did nothing about this it would find that it had "missed the boat."

Dr. Cheever asked what was Dr. Schadt's objection to using idle funds. Dr. Schadt replied that he was 100 per cent for the use of such funds as a means of financing the committee's proposal.

Dr. Allen G. Rice, Hampden, offered as an amendment to the amended motion the words "by drawing on the funds of the Society." This amendment was seconded by Dr. Parkins, and since it was accepted by Dr. Cheever, the maker of the original motion, and by Dr. Richardson, the seconder, it was declared by the President to be part of the original amendment.

Dr. Bagnall called on the Treasurer. Dr. Eliot Hubbard, Jr., Middlesex South. Dr. Hubbard said that the general fund stood at \$167,000, that the building fund stood at \$68,000 and that the latter fund could not be touched for the purpose under discussion.

Dr. Schadt pointed out that all the discussion about how the fund would be financed was not germane to the subject of the committee's first recommendation, which, he repeated, was simply that the Council authorize the establishment of a postwar loan fund. He added that the method of financing the fund would more properly come when the second recommendation was under discussion.

Dr. Chapin asked whether, if the amended motion prevailed, it would prevent the Council from immediately setting up this fund on the basis that necessity must be shown before the fund could be established. Dr. Bagnall said that he so understood the situation. He added that the establishment of such a fund in such a manner must also be contingent on the approval of the Finance Committee.

Dr. Richardson amended the amended motion so as to add the words "contingent on the approval by the Committee on Finance." This amendment was seconded by Dr. Cheever, who likewise accepted it as part of the original amendment.

Dr. Schadt again voiced his objection to the motion as amended.

The President called for a vote on the amendment, which was as follows:

That the Council of the Massachusetts Medical Society authorize the establishment of a postwar loan fund, when, as and if necessary and that this fund, contingent on the approval of the Committee on Finance, be established by drawing on the funds of the Society.

The amendment was carried by a show of hands — 35 for and 15 opposed. The motion as amended was put, and it was so ordered by vote of the Council.

At that point Dr. Schadt said that, in view of the action of the Council, no good purpose would be served by continuing the report.

Dr. Parkins moved,

That the Postwar Loan Fund Committee take this motion which we have passed to appropriate funds, evolve a program to use it, present it at the next Council meeting, with ways and means on how they would dispense it, and have the approval of the Committee on Finance and give us a working machine to handle it as they see fit.

This motion was seconded by Dr. Richardson.

In putting the motion, the President, with the apparent consent of Dr. Parkins, rephrased it so that the motion which was finally put was,

That this matter be referred back to the Postwar Loan Fund Committee to devise ways and means of carrying out the purpose of the motion just adopted.

It was so ordered by vote of the Council.

*Military Postgraduate Committee* — Dr. W. Richard Ohler, Norfolk, chairman.

This report, which was offered by the chairman, is as follows:

Since the meeting of the Council in October, seventy-two wartime postgraduate exercises have been given in twenty-two military installations by one hundred and ninety-five instructors. Since the formation of the New England Committee in June, 1943, a grand total of two hundred and eighty-one exercises have been conducted. Throughout this period, there has been maintained a fine spirit of co-operation between the various branches of the armed services and this committee, and there has always been a splendid response on the part of the instructors who have made this service possible. In this connection, I shall read from one of the many letters received by the committee: "I should like to convey to your committee sincere thanks and appreciation for the very fine lectures furnished us

during the time we have been here. I only trust that in our next assignments we can find a similar group of doctors who are interested in the continued education of the armed forces' physicians."

The question now arises, *How long is this work to continue?* In so far as your committee is concerned, we have taken the attitude that the work should continue as long as the armed services request it. Thus far, we have had no word to the contrary, and as a matter of fact, the usual allotment of funds has been made available recently by the American Medical Association, the American College of Physicians and the American College of Surgeons.

Nevertheless, during recent months, we have noted some falling off in enthusiasm on the part of certain Army and Navy installations, and this has naturally been reflected in the attitude of various groups of instructors. Unfortunately, owing to the change in the date of the Council meeting, it is necessary to render this report prior to a scheduled meeting of the New England Committee on February 2. We anticipate certain changes in the program and a curtailment of scheduled exercises. It is our hope that this work will not be allowed to die a lingering death, but that just as soon as it is apparent that this type of service is no longer needed it will be terminated by a directive from the armed services.

In the light of our present knowledge, it is recommended that the work of this committee be continued.

Dr. Ohler moved the acceptance of the report and the continuance of the committee. This motion was seconded by Dr. Cheever, and it was so ordered by vote of the committee.

#### *Medical Advisory Committee to Regional OPA —*

Dr. Joseph Garland, Suffolk, chairman.

The report, which was offered by the chairman, is as follows:

Since this committee last reported to the Council, drastic changes have taken place in food rationing. As of the first of the year, 85 per cent of all meat slaughtered went on the ration list, as compared with the 29 per cent that had been rationed since May, 1944, and the most popular canned vegetables, point-free since September, returned to rationing. At the same time, after a cancellation of outstanding points, the available red points per person were increased from  $7\frac{1}{2}$  to 12 weekly.

Examples have been presented by the OPA to show what the new basic ration will provide per week — for instance  $1\frac{1}{2}$  pounds of lamb chops and 1 pound of margarine, or 1 pound of liver and  $\frac{1}{4}$  pound of butter, or 1 pound of the choicest steak, or 1 pound of rib roast and  $\frac{1}{4}$  pound of butter, or 1 pound of bacon, 1 pound of lamb chops and  $\frac{1}{2}$  pound of margarine. The basic processed food ration will buy 1 pint of asparagus, beans or spinach, or  $\frac{1}{2}$  pint of applesauce, or  $\frac{1}{3}$  pint of peaches or peas.

In other words, the demands made on our food supply, the production of which is suffering from labor and transportation shortages, are going to cut fancy eating to a minimum, and we are going to understand a little more clearly, in this fourth year of war, that the Nation, as well as its armed forces, is in the battle.

This committee has not found it necessary to change its allotments, however; less indulgence will be found advisable, and, as no well person need suffer who is subsisting on basic rations, so, also, no ill person need suffer who is entitled to extra rations, up to a weekly total of 4 pounds of meat and fat, and a similar amount of processed foods.

Local rationing boards have had returned to them the power of granting extra rations, up to these prescribed limits, for those conditions originally recognized by the National Research Council, namely, diabetes mellitus, active tuberculosis, chronic nephritis of the nephrotic type, cirrhosis of the liver, severe hepatitis, chronic suppurative disease, severe burns and certain gastrointestinal conditions, such as those resulting from operations on the stomach, intestine or colon for ulcer or cancer, high intestinal fistulas, ulcerative colitis and sprue.

All other cases must be reviewed by or with the guidance of medical committees, local or regional, which shall decide which ones, for any of a variety of reasons, are to be made exceptions to the list compiled by the National Research Council, in order that no undue hardship shall result. Thus, your committee recognizes that certain bona-fide cases of allergy, rheumatoid arthritis, of anemia, epilepsy or any other condition in reason may require extra rations, but each must be decided on its own merits, with full knowledge of the facts available, and only for a limited period of time.

Butter and sugar must be recognized as luxury foods. So much of our total milk supply is being processed for overseas shipment that the amount available for the more uneconomic manufacture of butter is considerably reduced, and butter is available only at the fantastic point value of 24 per pound — double an individual's weekly point allowance. Equally nutritious fortified oleomargarine is available at 3 points per pound, and most people are going to learn to like it or go without. Unless acceptable evidence is presented that an applicant for extra fats must have butter, any extra allowance made is on the basis of margarine. Your committee feels sure that no one, after the casualty lists from the Battle of Belgium are made public, will consider this too great a sacrifice. We continue to recommend extra sugar rations only under the most exceptional circumstances, and the allowance of heavy cream, under the jurisdiction of the War Food Administration, has been reduced to 36 particularly needy cases.

Local advisory committees, appointed with the cooperation of the War Participation Committee, are functioning in Lawrence, Pittsfield, Springfield, New Bedford, Worcester and Brockton, in addition to those that have been locally appointed in other places.

Dr. Garland moved the acceptance of the report as one of progress. This motion was seconded by Dr. Ohler, and it was so ordered by vote of the Council.

#### *Committee on Maternal Welfare — Dr. Raymond S. Titus, Norfolk, chairman.*

In the absence of any member of the committee, the Secretary offered the report (Appendix No. 11) as published in the circular of advanced information. He moved its acceptance. This motion was seconded by Dr. Perkins, and it was so ordered by vote of the Council.

#### *Committee to Consider Expert Testimony — Dr. Frank R. Ober, Suffolk, chairman.*

No report.

#### *Committee on Physical Therapy — Dr. Arthur L. Watkins, Middlesex South, chairman.*

No report.

#### *Committee on Postgraduate Instruction — Dr. W. Richard Ohler, Norfolk, chairman.*

Dr. Ohler moved the discontinuance of the committee saying that its personnel had been taken over as a subcommittee of the Committee on Post-war Planning. This motion was seconded by Dr. Ober, and it was so ordered by vote of the Council.



*Committee on Council Rules* — Dr. Charles E. Mongan, Middlesex South, chairman.

This report, which was offered by Dr. Mongan, is as follows:

Dr. Elmer S. Bagnall, president of the Massachusetts Medical Society, appointed an *ad interim* committee, consisting of Charles E. Mongan, chairman, Frank R. Ober and Michael A. Tighe, whose purpose it was to study ways and means of improving the activities of and, if possible, shortening the time consumed by the Council.

In its initial report this committee recommends that there be set up certain rules for the conduct of the business of the Council.

The first three rules are as follows:

*Rule 1.* All new business offered at Council meetings shall be referred automatically by the President to the appropriate committee before action is taken by the Council.

*Rule 2.* All committee reports must be referred to the Executive Committee in advance of any Council meeting. Such reports shall be submitted at least six weeks before the Council meets. (This will provide opportunity for consideration by the Executive Committee in advance of the Council.)

*Rule 3.* These rules may be suspended, changed or discontinued on a majority vote of the Council.

By the latter rule, the above rules are made flexible. (For example, if a councilor wishes to present new business in a manner not in accordance with the above rule, he may move that the matter in mind may be acted on immediately under a temporary suspension of this rule. A majority vote of the Council authorizes such a temporary suspension.)

The Committee on Council Rules recognizes that three types of reports are offered to the Council: one that is purely informational, another that contains a recommendation or recommendations and still another that may have the character of both.

The Committee offers certain recommendations with regard to such reports, which it believes, if adopted, will further facilitate the work of the Council.

*Recommendation 1* (to be known as *Rule 4*). A report that is purely informational should contain a specific statement that it is being offered only for the information of the Council. At the completion of such a report, the person offering it should move its acceptance.

*Recommendation 2* (to be known as *Rule 5*). Reports that contain a recommendation should specifically state the recommendation. Its adoption should then be moved by the person offering the report. In the case of reports that contain several recommendations which are closely related and dependent, one on the other, the recommendations should be stated specifically in one, two, three order and their adoption should be moved by the person offering them. At the end of all reports containing recommendations, the persons offering them should move their adoption as a whole, subject to whatever change the Council has made in the recommendations.

*Recommendation 3* (to be known as *Rule 6*). In the case of reports that are informational as regards one subject and contain recommendations with regard to others, the principles outlined above should be followed in dealing with each part of the report.

Dr. Mongan moved the acceptance of the report. This motion was seconded, and it was so ordered by the Council.

Dr. Mongan moved the adoption of each rule and recommendation contained in the report. In each instance his motion was seconded, and it was so ordered by vote of the Council.

Dr. Mongan moved the adoption of the report as a whole. This motion was seconded by Dr. Ober, and it was so ordered by vote of the Council.

Dr. Mongan left the platform amid applause.

## NOMINATION OF DELEGATES

The President presented the following list of nominees as delegates:

*To the House of Delegates, American Medical Association, for two years, from June 1, 1945:*

### DELEGATES

Charles J. Kickham, Brookline  
Leland S. McKittrick, Boston

### ALTERNATES

John Fallon, Worcester  
Patrick J. Sullivan, Dalton

*To the House of Delegates, American Medical Association, for one year, from June 1, 1945:*

Dr. Patrick E. Gear, Holyoke, alternate to Dr. Charles E. Mongan, Somerville.

*To the annual meetings of the five New England state medical societies in 1945:*

*Maine:* Merrill C. Sosman, Boston; Frank R. Ober, Boston.

*New Hampshire:* Dwight O'Hara, Waltham; Howard F. Root, Boston.

*Vermont:* Frederick S. Hopkins, Springfield; George Ballantyne, Worcester.

*Rhode Island:* W. Richard Ohler, Jamaica Plain; Leroy E. Parkins, Boston.

*Connecticut:* Eugene M. Landis, Chestnut Hill; Charles F. Branch, Boston.

*To the Annual Congress on Medical Education and Licensure, American Medical Association, at the Palmer House, Chicago, February 12 and 13, 1945:*

Reginald Fitz, Boston.

Dr. Bagnall said that the appointment of delegates to the annual meetings of the other state medical societies was from the personnel of the Committee on Postwar Planning so that this committee might know what was going on in this respect in other states.

The President asked if there were any nominations from the floor. There being none, Dr. Ober moved that the nominations as read by the President be confirmed. This motion was seconded by Dr. Cheever, and it was so ordered by vote of the Council.

## Ad Interim APPOINTMENTS

Dr. Bagnall offered the following *ad interim* appointments:

### To the Council:

Dr. Alice M. Broadhurst, Middlesex South, replacing Dr. Stanton Garfield, resigned.

Dr. Ralph N. Brown, Middlesex South, replacing Dr. Brainard Conley, resigned.

Dr. Vlado A. Getting, Middlesex South, replacing Dr. Elliott Robinson, resigned.

Dr. William H. Blanchard, Suffolk, replacing Dr. William B. Breed, deceased.

Dr. William J. Elliott, Worcester, replacing Dr. Charles A. Sparrow, deceased.

Dr. William F. Regan, Middlesex East, replacing Dr. J. Harper Blaisdell, deceased.

### To the Committee on Publications:

Dr. John Fallon, replacing Dr. William B. Breed, deceased.

### To the Committee on Society Headquarters:

Dr. Frank R. Ober, chairman, replacing Dr. J. Harper Blaisdell, deceased.

Dr. Albert A. Hornor, a member, replacing Dr. Ober who has become chairman.



*To the Committee on Legislation:*

Dr. Edward J. O'Brien, representing Middlesex South, to replace Dr. Brainard F. Conley, resigned.

*To the Committee on Membership:*

Dr. Roy V. Baketel, replacing Dr. Sumner H. Remick, resigned.

*To the Committee on Postwar Planning:*

Dr. Howard F. Root, *chairman*; Dr. Leroy E. Parkins, *secretary*; Drs. Arthur W. Allen, Edward P. Bagg, George Ballantyne, Charles F. Branch, C. Sidney Burwell, Allan M. Butler, Nathaniel W. Faxon, Vlado A. Getting, G. Philip Grabfield, Frederick S. Hopkins, Chester M. Jones, Eugene M. Landis, Leland S. McKittrick, J. Howard Means, Robert N. Nye, Frank R. Ober, Dwight O'Hara, W. Richard Ohler, Walter G. Phippen, Merrill C. Sosman, Michael A. Tighe and Charles F. Wilinsky.

*To the Various Subcommittees of the Committee on Postwar Planning:*

*Co-ordinating Committee on Education:*

Drs. Charles F. Branch, Nathaniel W. Faxon and W. Richard Ohler.

*Subcommittee on Hospitals:*

Dr. Nathaniel W. Faxon, *chairman*; Drs. Arthur W. Allen, James W. Manary and Charles F. Wilinsky.

*Subcommittee on Medical Economics:*

Dr. Leland S. McKittrick, *chairman*; Drs. Allan M. Butler, Vlado A. Getting and Merrill C. Sosman.

*Subcommittee on Medical Schools:*

Dr. Charles F. Branch, *chairman*; Drs. C. Sidney Burwell, Dwight O'Hara and Walter G. Phippen.

*Subcommittee on Organization:*

Dr. Chester M. Jones, *chairman*; Drs. Edward P. Bagg, George Ballantyne, Frederick S. Hopkins, J. Howard Means, Frank R. Ober, Joseph W. O'Connor, Francis J. Steele and Michael A. Tighe.

*Subcommittee on Postgraduate Education:*

Dr. W. Richard Ohler, *chairman*; Drs. Vlado A. Getting, G. Philip Grabfield, Edward G. Huber, Lewis M. Hurxthal, Charles J. Kickham, Eugene M. Landis, Robert N. Nye, Frank R. Ober, Joseph W. O'Connor and Samuel H. Proger.

*To the Committee on Rehabilitation:*

Dr. Joseph H. Shortell, *chairman*, replacing Dr. William E. Browne, resigned.

*To the Committee on Council Rules:*

Dr. Charles E. Mongan, *chairman*; Drs. Frank R. Ober and Michael A. Tighe.

Dr. Bagnall spoke of the resignation of Dr. Conley as chairman of the Committee on Legislation as having come about because of his change of residence.

Dr. Cheever moved the Council's approval of these appointments. This motion was seconded by Dr. Ober, and it was so ordered by vote of the Council.

Dr. Charles J. E. Kickham, Norfolk, expressed the belief that the Subcommittee on Hospitals of the Committee on Postwar Planning should be more representative of all the hospitals of Massachusetts. He pointed out that, as it was constituted, only the three main hospitals in Boston were represented. He expressed the belief that this condition should be remedied by making certain additions to this subcommittee.

Dr. Root said that it was planned to do just that. He added that, if the previous speaker would send in to the committee the name of a hospital representative who would be willing to attend meetings and participate in the job ahead, that name would be added. Dr. Kickham said that he had no particular person in mind.

## OBITUARIES

Obituaries of former councilors were read by the President as follows:

DR. JOHN HARPER BLAISDELL, a member of the Council from Middlesex East District since 1931, died suddenly on October 25, 1944, in Boston. He was in his fifty-ninth year.

Dr. Blaisdell was graduated in 1907 from Dartmouth College and received his degree in medicine from the Harvard Medical School in 1911. After his internship at the Massachusetts General Hospital he began practice in Boston, specializing in dermatology. He taught for many years at the Harvard Medical School and was a member of the staffs of the Massachusetts General Hospital and the Boston Dispensary.

He had long been prominent in the affairs of the Massachusetts Medical Society having held the following positions: vice-president and president of the Middlesex East District Medical Society; a member of the Committee on Public Relations since its organization in 1931 and chairman of its Subcommittee on Hospital Relations; nominating councilor from Middlesex East District in 1932 and alternate nominating councilor for several years; secretary and chairman of the Section of Dermatology and Syphilology; chairman of the Committee to Revise the By-laws, which was established in 1942; chairman of the Committee on Society Headquarters; a member of the Committee Concerned with Prepayment Medical-Care Costs Insurance; and, finally, just before his death, chairman of the newly formed Committee on Council Rules.

Dr. Blaisdell was one of the prime movers in the organization and administration of the Massachusetts Hospital Service Corporation (Blue Cross) and the Massachusetts Medical Service Corporation (Blue Shield). He was one of the original signers of the charter granted the Massachusetts Hospital Service Corporation on March 11, 1937. He served as a member of the Board of Directors of the Blue Cross from 1937 until his death. He also served as a member of the Board of Directors of the Blue Shield from the time of its organization in 1942 until his death. He was chairman and joint representative for the Massachusetts Medical Service and the Massachusetts Hospital Service on the Interlocking Services Committee.

His memberships included the American Medical Association, American Dermatological Association, New England Dermatological Society, of which he was at one time president, and the Atlantic Dermatological Conference. He was formerly chairman of the Section of Dermatology and Syphilis of the American Medical Association.

Dr. Blaisdell is survived by his widow and two sons.

DR. ALFRED J. BONNEVILLE, of Hatfield, died January 11. He was in his seventy-fourth year.

Dr. Bonneville received his degree from the Medico-Chirurgical College of Philadelphia in 1911. He was vice-president of the Hampshire District Medical Society in 1920 and president of this district in 1921. He was district supervising censor and councilor of the Society from 1922 to 1945, and a member of the Committee on Public Relations from 1942 to 1945.

In 1944, Dr. Bonneville was cited by Governor Saltonstall for his work in civilian defense. He was on the staff of the Cooley Dickinson Hospital, Northampton, and was a fellow of the American Medical Association.

His widow and three sisters survive.

DR. GEORGE B. FENWICK, of Chelsea, died October 27. He was in his sixty-eighth year.

Dr. Fenwick graduated from Harvard University in 1900 and from Harvard Medical School in 1904. He was

a member of the local Selective Service board and organized the Civilian Defense Medical Unit in Chelsea. He served several terms on the Chelsea Board of Health. He had been a member of the Council from Suffolk District since 1936.

His widow, a daughter and a son survive.

At the request of the President, the Council stood for one minute in silent tribute to the memory of these former councilors.

### NEW BUSINESS

Dr. Reginald Fitz, Suffolk, directed a question to Dr. Mongan, chairman of the Committee on Council Rules, as to what was meant by the words "majority vote of the Council" as these words appear in the rules that had been adopted. Dr. Mongan replied that this meant a majority of those present.

There being no further business before the Council, the President announced the meeting adjourned at 5:20 p.m.

MICHAEL A. TIGHE, *Secretary*

### APPENDIX NO. 1

#### ATTENDANCE OF COUNCILORS

##### BARNSTABLE

C. H. Keene  
J. G. Kelley  
W. D. Kinney

##### FRANKLIN

H. M. Kemp  
W. J. Pelletier

##### BERKSHIRE

I. S. F. Dodd  
C. F. Kernan  
F. R. Smith  
P. J. Sullivan

##### HAMPDEN

M. J. Bachulus  
E. P. Bagg  
W. A. R. Chapin  
E. C. Dubois  
G. D. Henderson  
M. W. Pearson  
A. G. Rice  
G. L. Schadt  
G. L. Steele

##### BRISTOL NORTH

W. H. Allen  
R. M. Chambers  
W. J. Morse  
J. L. Murphy  
W. M. Stobbs

##### HAMPSHIRE

L. B. Pond

##### BRISTOL SOUTH

G. W. Blood  
E. D. Gardner

##### MIDDLESEX EAST

Richard Dutton  
E. M. Halligan  
R. W. Layton  
M. J. Quinn  
W. F. Regan  
R. R. Stratton

##### ESSEX NORTH

E. S. Bagnall  
R. V. Baketel  
J. T. Batal  
G. J. Connor  
Elizabeth Councilman  
H. A. Fenton  
E. H. Ganley  
P. J. Look  
R. C. Norris  
G. L. Richardson  
F. W. Snow  
C. F. Warren

##### MIDDLESEX NORTH

H. R. Coburn  
W. M. Collins  
D. J. Ellison  
A. R. Gardner  
W. F. Ryan  
M. A. Tighe

##### ESSEX SOUTH

H. A. Boyle  
C. L. Curtis  
Loring Grimes  
P. P. Johnson  
A. E. Parkhurst  
O. S. Pettingill  
W. G. Phippen  
E. D. Reynolds  
G. S. Rust  
P. E. Tivnan  
C. F. Twomey  
C. A. Worthen

##### MIDDLESEX SOUTH

E. W. Barron  
W. B. Bartlett  
Harris Bass  
J. D. Bennett  
W. O. Blanchard  
G. F. H. Bowers  
Alice M. Broadhurst  
Madeline R. Brown  
R. N. Brown  
R. W. Buck  
E. J. Butler  
J. F. Casey  
J. A. Daley  
H. F. Day

C. W. Finnerty  
H. Q. Gallupe  
F. W. Gay  
V. A. Getting  
H. G. Giddings  
H. W. Godfrey  
J. L. Golden  
A. D. Guthrie  
Eliot Hubbard, Jr.  
F. R. Jouett  
A. A. Levi  
A. N. Makechnie  
C. E. Mongan  
I. P. Nelligan  
E. J. O'Brien, Jr.  
Dwight O'Hara  
Fabyan Packard  
L. G. Paul  
T. E. Reilly  
Max Ritvo  
M. J. Schlesinger  
E. W. Small  
H. P. Stevens  
A. B. Toppan  
J. E. Vance  
C. F. Walcott  
A. L. Watkins  
B. M. Wein  
Hovhannes Zovickian

##### PLYMOUTH

S. J. Beers  
C. H. King  
P. H. Leavitt  
C. D. McCann  
J. J. McNamara  
B. H. Peirce  
W. H. Pulsifer

##### SUFFOLK

W. H. Blanchard  
W. J. Brickley  
W. E. Browne  
David Cheever  
Pasquale Costanza  
N. W. Faxon  
Reginald Fitz  
Maurice Fremont-Smith  
Channing Frothingham  
Joseph Garland  
F. C. Hall  
John Homans  
A. A. Hornor  
L. M. Hurxthal  
W. J. Mixer  
Donald Munro  
H. L. Musgrave  
H. F. Newton  
R. N. Nye  
F. R. Ober  
F. W. O'Brien  
J. P. O'Hare  
L. E. Parkins  
L. E. Phaneuf  
Helen S. Pittman  
J. H. Pratt  
W. H. Robey  
R. M. Smith  
M. C. Sosman  
E. F. Timmins  
J. J. Todd  
S. N. Vose  
Conrad Wesselhoeft

##### WORCESTER

C. R. Abbott  
A. W. Atwood  
George Ballantyne  
Gordon Berry  
W. P. Bowers  
E. J. Crane  
J. J. Dumphy  
W. J. Elliott  
John Fallon  
L. M. Felton  
L. P. Eloland  
W. F. Lynch  
J. C. McCann  
A. E. O'Connell  
H. L. Paine  
R. S. Perkins  
O. H. Stansfield  
T. L. Story  
R. J. Ward  
B. C. Wheeler

##### WORCESTER NORTH

H. D. Bone  
J. V. McHugh  
F. A. Reynolds  
B. P. Sweeney

Total 207

##### NORFOLK

Carl Beare  
Arthur Berk  
M. I. Berman  
J. H. Carey  
William Dameshek  
G. L. Doherty  
Albert Ehrenfried  
H. M. Emmons  
Susannah Friedman  
B. A. Godvin  
J. B. Hall  
H. B. Harris  
R. J. Heffernan  
H. J. Inglis  
P. J. Jakmauh  
C. J. E. Kickham  
H. M. Landesman  
D. S. Luce  
C. M. Lydon  
D. L. Lynch  
F. P. McCarthy  
H. L. McCarthy  
F. J. Moran  
M. W. O'Connell  
W. R. Ohler  
G. W. Papen  
H. S. Petterson  
S. A. Robins  
I. A. Seth  
Kathleyne S. Snow  
J. W. Spellman  
M. H. Spellman  
W. J. Walton

##### NORFOLK SOUTH

D. L. Belding  
Harry Braverman  
N. R. Pillsbury  
D. B. Reardon  
H. A. Robinson

### APPENDIX NO. 2

#### PROPOSED AMENDMENT TO THE BY-LAWS

The following amendment to the by-laws of the Massachusetts Medical Society is submitted by Dr. Jacob Fine:

Chapter V, Section 2b, is hereby amended to read as follows: The secretary of a district society shall receive an application from a graduate of a discontinued medical

school, a foreign medical school after the year 1933 or any medical school not approved by the Council only, when the applicant has possessed a license to practice medicine in the United States or its territories for at least five years. A graduate of a foreign medical school on the approved list of the National Board of Medical Examiners prior to 1934 may apply for membership to the secretary of a district society if he has possessed a license to practice medicine for a minimum of five years.

Dr. Fine offers in support of this amendment the following:

If the administration of this modification of the 1942 amendment would be difficult, I would ask the Executive Committee to consider reverting to the wording of this section of the by-laws prior to May, 1942. At the annual meeting of the Massachusetts Medical Society in May, 1942, an amendment to the by-laws was adopted under Chapter V, Section 2b, which reads as follows:

The secretary of a district society shall receive an application from a graduate of a discontinued medical school, a foreign medical school or any medical school not approved by the Council only when: The applicant has possessed a license to practice medicine in the United States or its territories for at least five years.

This amendment to the by-laws is a modification of a previous amendment adopted in 1939, which specified that eligibility for membership of applicants from such medical schools required practice for a minimum of five years. The 1939 amendment did not specify that the practice must have been within the confines of the United States or its territories. The reason for the adoption of the 1939 amendment, according to the Committee on Membership in its report of May 22, 1944, was that "an increasing number of physicians were beginning to infiltrate Massachusetts." When the more restrictive amendment of 1942 was presented to the Society the spokesman for those in favor stated that there was "nothing revolutionary as it appears in the text." He read the 1939 amendment for comparison with the 1942 amendment showing the distinction mentioned above. He added as the reason for the change that applicants for membership should have lived in their community sufficiently long to afford their conferees opportunity to pass on their standards of practice. Many of those who opposed the 1942 amendment felt that such a reason for adopting the change was discriminative, since if it requires five years to evaluate a physician's standards of practice, why should we customarily admit those trained in the United States shortly after their entry into practice? The implication from the spokesman's statement is that the ethics and the training of the European physicians are necessarily subject to greater scrutiny than those of native physicians.

It is therefore pertinent to inquire into the ethics and training of the foreign physician. As for the training of European physicians, some doubt that European schools during the last decade have been able to provide adequate training. The Committee on Membership stated in its May, 1944, report to the Council that no one knows how good an education foreign physicians had received and that the Committee on Medical Education found it "impossible to evaluate the medical education in foreign schools, particularly that gained on the Continent." According to the Committee on Membership, the Council on Medical Education and Medical Diplomas until 1939 had been determining what foreign medical schools were acceptable as offering an education equivalent to that of our recognized domestic schools. In actual practice, however, the Committee on Medical Education and Medical Diplomas did not undertake to evaluate foreign medical schools, but considered each applicant's qualifications on an individual basis. Data on foreign medical schools, however, was available to this committee, if such was needed, from the list of foreign medical schools published by the National Board of Medical Examiners as having acceptable standards. Since the Massachusetts Board of Registration in Medicine accepts diplomates of the National Board without further examination, it is fair to assume that the latter's standards for admission to examination are acceptable in Massachusetts. If this list became of doubtful value after 1933, the year when the European turmoil suddenly became aggravated due to the rise of Hitler, it was still valid for physicians who had graduated from medical schools before that time. Why should

such physicians, whose type of education was known and approved by the National Board of Medical Examiners be classed with those whose education obtained at a later time might be considered of dubious quality? Why is it not fair and proper to distinguish between graduates from foreign schools before and after 1933?

The Committee on Membership cites as evidence of the poor education of foreign-trained physicians their poor showing in the State Board examinations compared with that of native physicians. Any open-minded person will admit that any physician over forty (the minimum average age of medical emigres) not facile in the English language and psychologically traumatized could hardly be expected to do better. What is more appropriate for consideration by the Society is not the doctors who failed but those who passed. Shall those who passed be penalized because others failed?

One may speculate as to other motives than those alleged, which may have been responsible for the 1942 amendment. The Committee on Membership states that in 1939 foreign physicians "began to infiltrate Massachusetts" and the number who came in per year was mounting rapidly, totaling over three hundred according to the Committee on Membership, although the *American Medical Directory* and the files of the Boston Committee on Medical Emigres did not show much more than about half this number in actual practice in this state up to 1942. Is it not reasonable to assume that numbers, not qualifications, comprised the stimulus for this amendment? Even the larger figure indicates how trifling those numbers have been in proportion to the total number of physicians in this state. The Committee on Membership agrees that there will be an occasional foreign-educated physician on whom the five-year rule will work a hardship. Obviously, if no hardship were involved, this discussion would serve little more than an academic purpose. The fact, however, is that most of the foreign physicians who practice in small and many of those in large communities do not have hospital privileges because they are told they are not members of the Massachusetts Medical Society. This is a hardship which the 1942 amendment is working, and it is a real hardship, ample testimony for which is available to the Boston Committee on Medical Emigres and anyone else interested.

As for the ethics of foreign physicians, if some will say that it was not numbers but dubious ethics which brought about the 1942 amendment, I would ask them to state the evidence, not in general terms, innuendo or hearsay, but by specific case histories and the number of such instances before and since the adoption of the 1942 amendment, which could justify continuation of the amendment in its present form. I am sure it can be shown that the foreign-trained physician has behaved neither better nor worse than native physicians and that he should be so regarded from the point of view of the time when he should be eligible for membership in this society.

## APPENDIX NO. 3

### REPORT OF THE COMMITTEE ON PUBLICATIONS

The Committee on Publications wishes to record its sense of great loss in the death of Dr. William B. Breed. Dr. Breed contributed to the deliberations of the committee a broad vision, mature judgment and unflinching good will.

The committee has invited Colonel Walter Bauer, medical consultant to the Eighth Service Command to deliver the Shattuck Lecture. The invitation has been accepted subject to the exigencies of military duty.

The committee recommends the publication of the *Directory* for the year 1945. No directory has been published since 1942, and because many changes have occurred in the fellowship list since that time, the officers believe that there is a distinct need for a new directory. It recommends, however, that the printing be limited to 500 copies and that they be distributed to the members of the Council and to other members in good standing on request. It is recommended that \$1500 be appropriated for this purpose.

The committee has continued to supervise the publication of the *New England Journal of Medicine*. Again we wish to record our deep appreciation to the managing editor, Dr. Robert N. Nye, for his efficient management of the *Journal*. We should also like to commend the work of Miss

Davies and her assistants, who have accomplished a phenomenal task under most trying circumstances.

During 1944, the *Journal* received 6109 new "outside" subscriptions, a figure 42 per cent greater than that for 1943. Of these, 4221 were from regular subscribers, and 1888 from students. There were many cancellations, and the net increases were 2394 and 357, respectively. Of the 1531 student subscriptions that expired, it is interesting that 674 were renewed at the full rate. As of December 31, journals were being sent to 4517 members of the Society (including 288 in military service), 7512 regular subscribers, 2371 medical students and 348 miscellaneous readers, a grand total of 14,885, not including 337 copies sent once a month to members of the New Hampshire Medical Society. This is an increase of 2652 over the corresponding figures for 1943, in spite of a decrease of 240 in copies going to members of the Massachusetts and New Hampshire medical societies.

Operations for the year resulted in a net loss of \$7937, which is accounted for by cash payments totaling \$7900 from the Society and a loss of \$37 in total assets or surplus. This compares with a loss of \$5852 in 1943. The increase in expense, which is greater than would be expected because of increase in circulation, was occasioned by larger costs for printing and binding. The net cost for each active member of the Society was \$1.81, compared with \$1.30 in 1943.

The editorial board considered 194 manuscripts during 1944, of which 151 were accepted, a slight reduction over the figures for 1943, which were 211 and 162, respectively. This has, of course, cut down the pagination devoted to original articles, but such a policy has seemed to be more desirable than the acceptance of papers that do not meet the standards set by the editorial board.

The *Journal* is still troubled by the paper shortage. We were able this year to continue publication because of an extra allowance of paper from the War Production Board, owing to the fact that so many journals were sent to military organizations and men in military service, and by reducing the weight of paper stock. The year 1945 presents unusual difficulties in relation to paper supply. It will be necessary to receive another ex-quota allotment from the War Production Board and possibly to use a lighter weight of paper.

The Council will remember that a year ago the Committee on Publications reported that a change had been made in the firms responsible for the printing, binding and mailing of the *Journal*. It was hoped that this change would overcome some of the difficulties that had been present in previous years because the former printer was unable to do satisfactory work. The change in printers obviously presented many annoying and time-consuming incidents because of the new printer's unfamiliarity with many of the details. It was hoped that these difficulties would decrease as the year advanced. They are, however, still present. The reprints have been delayed, much as before. There has been continued difficulty with the mailing stencils, and this has necessitated increased work by the clerical staff. These difficulties we hope will be ironed out in the course of time. If the *Journal* continues to increase its circulation and the office work continues to expand, additional space will soon be needed.

Because of the increasing circulation outside of Massachusetts, about the first of the year a form letter with a return post card was sent to subscribers in four widely separated sections of the United States—Connecticut, Ohio, Texas and two West-Coast states, Oregon and Washington. The letter requested that the subscriber indicate on the post card his choice of various features of the *Journal* and whether or not he would probably subscribe if the progress reports were reprinted as a quarterly publication. The preliminary tabulation of replies indicates that by far the majority of these readers subscribe to the *Journal* because of its total content and that the case reports are the most popular of the individual features. The response to the question concerning the quarterly reprinting of the progress reports appears to indicate that such an undertaking would be successful.

The outlook for 1945 is difficult to visualize. The shortage of book paper may necessitate a further cut in the size of the *Journal*. Our difficulties with printing, binding and mailing may become less troublesome. Advertising contracts promise to bring in a larger net return than ever before; the rates were again increased on January 1, and those of

January 1, 1944, become effective for the advertisers whose contracts were extended a year ago at the 1943 rate. There is no appreciable letup in the increase of circulation, although the net increase will probably be less than in 1944. Operating costs should increase only proportionally with the circulation, and because of the increase in revenue, the net cost to the Society should be lower. On account of unpredictable factors, however, an appropriation of \$8000 has been requested.

The accounts of the *Journal* have been audited and found to be in order.

RICHARD M. SMITH, *Chairman*

## APPENDIX NO. 4

### REPORT OF THE COMMITTEE ON PUBLIC HEALTH BASIC GENERAL PLAN FOR A MASSACHUSETTS PROGRAM FOR THE CARE OF CHILDREN WITH ACUTE RHEUMATIC FEVER

It is intended that the proposed acute rheumatic fever program as described in the following pages shall be conducted as a part of Services for Crippled Children. There are several good reasons for including such dissimilar conditions as orthopedic and plastic cases with acute rheumatic fever in one administrative unit other than that the funds for all those conditions emanate from the Children's Bureau of the Department of Labor. The most important reason is that the members of the Department of Public Health who are conducting Services for Crippled Children have, during the eight years that the Service has been in operation, maintained excellent relations with the members of the Massachusetts Medical Society, both individually and collectively.

The acute rheumatic fever program will be administered as nearly in accordance with the principles that have guided the conduct of Services for Crippled Children as is possible, taking into consideration the clinical differences between the two types of patients. The same high ethical standards will be maintained and professional standards will be equally high.

No children will be accepted for care under the acute rheumatic fever program unless a request for such care signed by a licensed physician has been received and unless a social service worker has investigated the home and has determined the fact that the family is medically indigent. A patient having been accepted for care will be given medical and hospital care, and care in a convalescent home, if necessary. The program will be limited to children of school age, and no custodial care for children with far-developed heart disease will be provided. The same relations will be maintained with the family physician as has been done in Services for Crippled Children, that is, the patient is always regarded as having been merely referred to the department for special services. The family physician will be kept informed of the progress of his patient and the patient will be referred back to him on discharge.

It will be recalled that the Department of Public Health in 1936, after state-wide conferences with members of the respective district medical societies, obtained the approval of the Council of the Massachusetts Medical Society for the conduct of the Crippled Children's program. The Department of Public Health intends to conduct the rheumatic fever program under the same basic policy as has always been in effect, namely, that there will be no infringement upon the rights of practicing physicians. All children accepted for care under the Crippled Children's program have invariably presented an application signed by a physician.

It is desired to secure the authority of the General Court so that hospitalization and convalescent care for the majority of the children cared for under the program can be provided at the North Reading State Sanatorium. It is also planned to purchase hospital care in other hospitals in the state for children whom it would be preferable to hospitalize locally because of transportation difficulties, or for social or other reasons. Similarly, convalescent care would be provided elsewhere whenever necessary.

About fifteen states now have programs in operation for the care of children with acute rheumatic fever or heart disease, but in only one of these states is the program state-wide. The Children's Bureau has, however, indicated that a state-wide program for Massachusetts would be acceptable. Such a program in order to receive the approval of the chief

of the Children's Bureau and at the same time to meet the needs of the Commonwealth must be organized and administered along the following lines.

1. *Administration of the program.* — The administration of a Massachusetts rheumatic fever program should be the responsibility of the Orthopedic Bureau of the Division of Child Hygiene of the Department of Public Health. A pediatrician with special knowledge of this field should assume direct responsibility for planning and developing these services. An advisory committee should be appointed by the Commissioner of Public Health, which should be composed of representatives of the various professional fields involved in a program of this type — medical, social, nursing, education and so forth.

2. *Eligibility for care.* — Children under the age of twenty-one with heart disease or conditions leading to heart disease, who are medically indigent, are eligible for care. Emphasis would be given to the care of children with rheumatic fever or rheumatic heart disease; particularly early in the disease, but children with other types of heart disease which offer a reasonable expectation of improvement through treatment should also be eligible for care. Mere custodial care would not be authorized. As in the case of children with orthopedic or plastic defects, diagnostic services would be available, on the signed request of a registered physician, to all children of the Commonwealth, but a child would be accepted for further care only when it has been determined (as is done at present) that the child's family is unable to meet, in whole or in part, the expenses of prescribed treatment.

3. *Basic professional services.* — a. *Medical services.* — A pediatrician employed by the Department of Public Health on a full-time basis would be administratively responsible for medical care of these children in all stages of treatment, whether in clinic, hospital, convalescent home, foster home or the child's own home. This would ensure continuity of medical care. This pediatrician should either have already had special training or experience in the field of rheumatic fever and heart disease in children or should be given special training in this field. Consultation services by cardiologists, surgeons and specialists in other branches of medicine and surgery would be provided when necessary by qualified consultants who are certified by, or eligible for certification by, the boards of their respective specialties. Fees for such services would be paid by the Department of Public Health.

b. *Medical-social services.* — Medical-social consultants on the staff of the Department of Public Health would be responsible for meeting the medical-social needs of these children. These workers would not merely give direct service in connection with all phases of the care of the children but their function would be largely that of developing and helping to improve the social services available in the community to those children.

c. *Public-health nursing services.* — A public-health nursing consultant on the staff of the Department of Public Health would supervise the public health nursing services for children under this program. Generalized public-health nursing services are more widely available in Massachusetts than in almost all other states, so that a state-wide program could be easily administered.

4. *Diagnostic services.* — Diagnostic services would be provided in clinic centers, as is done in the orthopedic consultation clinics. If, for diagnosis, observation or any procedure too elaborate for the clinic is necessary, the children would be hospitalized for diagnosis. Diagnostic service would be arranged for by the Department of Public Health pediatrician. If a child who needs diagnostic service is too sick to come to the clinic, the pediatrician would make a home visit, in consultation with the family physician.

5. *Treatment services.* — a. *Clinic services.* — Regular clinics would be held for diagnostic services and follow-up care. These clinics would be conducted by a pediatrician, assisted by a medical-social worker and a public-health nurse. Not more than six or eight children would be seen in a half-day clinic session.

b. *Hospital care.* — The Department of Public Health will seek legislation authorizing the admission of children suffering from rheumatic fever and heart disease to the North Reading State Sanatorium. It is also planned to purchase hospital care in other hospitals in the state for children whom it would

be preferable to hospitalize locally because of transportation difficulties, or for social, or other reasons.

c. *Convalescent care.* — Children would be kept in hospital only during the acute stage of the disease and would then be transferred elsewhere for a period of prolonged bed rest during the chronic stage. This type of care is usually provided in a convalescent home, a foster home, or the child's own home.

(1) *Convalescent home care.* — At these homes medical, nursing and social supervision adequate for the care of the sick child in bed would be given. Such homes would also be used for children who have entirely recovered from rheumatic fever but who are not physically up to par because of the recent acute attack. It is probable that a portion of the North Reading State Sanatorium could be set aside for this type of care.

(2) *Foster-home care.* — Occasionally, foster homes are the only resource available, although experience in Services for Crippled Children indicates that this service is not often needed. This type of care seems preferable to institutional care for some individual children.

(3) *Care in the child's home.* — Services in the child's own home include diagnostic services for the child who is physically unable to attend a clinic and treatment for the child with rheumatic fever or a complicating illness if he can be cared for in his own home. Joint planning by the pediatrician, the medical-social consultant and the public-health nursing consultant would be necessary to meet any personal and environmental difficulties which might obstruct the treatment and care of the child in the home situation.

6. *Transportation of children.* — This can usually be arranged in co-operation with local community agencies. Ambulance service would need to be provided by the Department of Public Health when necessary.

7. *Educational needs of the rheumatic child.* — Social Security funds are not provided for education of the physically handicapped child, but medical-social workers would be expected to arrange for such services through official educational agencies.

8. *Vocational guidance.* — There is already a close relation between the Department of Public Health and the Division of Vocational Rehabilitation of the Department of Education for vocational guidance for crippled children. This co-operation would be extended to the children cared for in an acute rheumatic fever program.

ROY J. WARD, *Chairman*  
ERNEST M. MORRIS, *Secretary*

## APPENDIX NO. 5

### REPORT OF THE COMMITTEE ON SOCIETY HEADQUARTERS

A meeting of this committee was held on June 7, 1944, the chairman, Dr. J. H. Blaisdell, presiding. There were present Drs. D. B. Reardon, F. R. Ober, M. A. Tighe, R. Fitz and E. S. Bagnall. The space occupied by the Society and the *New England Journal of Medicine* was inspected. Following this, there was a discussion of the duties of the committee and what funds were available for carrying out those duties. It was voted that the chairman, together with the Treasurer and the chairman of the Committee on Finance, should look into the question of what money is available to this committee and what charges should be made against it, and also to report on how and what rent is paid to the Boston Medical Library, reporting their findings back to the Committee on Society Headquarters.

A second meeting of this committee was held on October 25, at 1:15 p.m. There were present Drs. Tighe, Ober and Reardon of the committee and also Drs. R. N. Nye, R. M. Smith, F. C. Hall and Eliot Hubbard and Mr. R. St. B. Boyd. In the absence of the chairman, Dr. Blaisdell, Dr. Ober called the meeting to order. Dr. Nye explained that the purpose of the meeting was to consider the item in the budget labeled "Headquarters." The money in this item although spent was never approved by any committee, which is required by the by-laws. It was explained that the chairman of the committee, Dr. Blaisdell, thought this ought to be a function of the Committee on Society Headquarters. Under this budget would be included miscellaneous items, clerical assistance for various committees and so forth. It was ex-

plained that this sum should be split up and allocated to its proper authorities. Such items as rental, cleaning and lighting should be charged to the Committee on Society Headquarters, and the remainder of the charges should be under a separate heading and charged to the Secretary's expenses, allowing an additional budget of about \$6000 a year to cover such expenses. This would be a more businesslike procedure and would also be according to the by-laws of the Society. It was suggested that the heading for this item be called "Administration Expenses."

It was voted to set up a budget for general administrative expenses for the Massachusetts Medical Society and that this fund should be in the hands of the officers of the society.

At that point in the meeting word was received that Dr. Blaisdell, chairman of the committee, had just been killed in an automobile accident. The meeting was then adjourned.

On November 1, Dr. Ober was appointed chairman of the committee, and later on Dr. A. A. Hornor was appointed to fill the vacancy that had occurred as a result of the death of Dr. Blaisdell. The office space occupied by the Massachusetts Medical Society was inspected and measured. It was found to be in need of furniture and other accessories to make it useful to the Society. A budget was made out covering the estimated cost of these necessary items and was submitted to the Committee on Finance. This sum will appear in the report of the Committee on Finance.

FRANK R. OBER, *Chairman*

## APPENDIX NO. 6

### REPORT OF THE COMMITTEE ON FINANCE

The Committee on Finance met on December 13, 1944, at the Headquarters of the Massachusetts Medical Society, 8 Fenway. Present were Drs. Peer P. Johnson, Ernest L. Hunt and Francis C. Hall as members of this committee. Also present were President Elmer S. Bagnall, Secretary Michael A. Tighe and Treasurer Eliot Hubbard, Jr.

At this meeting the committee noted the amount and nature of our income for 1944 — \$59,629.26. A list of the items from which we derived this income is set forth below. The committee set up a budget for the fiscal year of 1945 — a figure of \$52,960.00. This budget is set forth below. We noted the sales and purchases of investments by the Treasurer carried out on the advice of Loomis and Sayles, investment counselors. We noted also the expenses submitted by the different committee chairmen.

It will be noted that our income is slightly larger than last year despite the further falling off in the item of dues of \$3110. This falling off in the amount from dues, owing to remissions given to doctors going into the service, is less than before, and should not decrease very much from now on. The increased income is largely due to an increase in the amount coming to us from investments and seems to justify our employment of expert investment counselors. Our budget for 1945 is well within our estimated income. It is \$6000 larger than that for 1944, owing to increases in three items of expense. The first is the setting up of a Bureau of Clinical Information at Society Headquarters estimated at \$2800 for maintenance. The second is the setting up of the Committee on Postwar Planning, which plans to be very active, with a cost estimated at \$3000. The third is the increased habit of committees to have dinner meetings. Unquestionably dinner meetings result in better attendance of members and are fair to the men coming to Boston from a distance. This custom should result in benefit to the Society if used with discretion.

Again, the Committee on Arrangements brought in a surplus instead of a deficit, due in large part to the efficiency of our executive secretary, Mr. Boyd, in selling booths to advertisers wishing to exhibit at the annual meeting and due to increased charges for these booths. The profit last year was \$3542. For three successive years the chairmen of the Committee on Arrangements have recommended that Mr. Boyd's salary be increased because of the fact that over a period of some years now his efforts have resulted in a change from a marked deficit to a real profit. They also pointed out that Mr. Boyd has taken on more and more work in relation to the activities of the various committees. He is giving all his time to the work of the Massachusetts Medical Society. The Committee on Finance recommends that his salary be

increased to \$4000, and that more opportunities be given Mr. Boyd to serve the Society by having him sit in on committee meetings and carry out the wishes of the committees, and by studying the methods of running other state medical societies.

Dr. Robert N. Nye continues to run the *New England Journal of Medicine* with such efficiency that subscriptions are continuing to increase, advertising rates have been raised, and the cost of the *Journal* to the Society is less each year. In 1944 instead of requiring the \$13,000 allotted to the *Journal* in the budget, Dr. Nye required only \$7000. He is asking for only \$8000 next year, and probably will not need to use this amount.

We recommend the setting up of a special item under General Administrative Expense with a budget of \$2000, this fund to include expenses for stenography, telephone and innumerable items plus extraordinary expenses which have previously been assigned to Society Headquarters as separate from the Committee on Society Headquarters. This does not constitute extra expense but assigns these items to the care of the President and Secretary, leaving to the Committee on Society Headquarters merely the definite items of rent, light, heat and cleaning of the Headquarters rooms. The type of items included under Administrative Expense will be assigned to committee so far as possible, and we hope that a large part of this budget will be unexpended, but in the past no one has been responsible for them.

It seems to the committee that the Society is being run with increasing efficiency and conservatively so far as expenditures are concerned. The investment portfolio seems to be in sound hands.

FRANCIS C. HALL, *Chairman*

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### DETAILED LIST OF 1944 INCOME

Shattuck Fund .....	\$183.34
Phillips Fund .....	300.00
Cotting Fund .....	50.00
Building Fund .....	1898.30
General Fund .....	4213.87
Brickley Fund .....	15.00
Nonresident dues .....	149.00
Annual dues (39,999 and Dec. estimate 600) .....	39,699.00
Directors' examinations .....	12.00
Censors' examinations .....	228.00
Committee on Arrangements .....	11,535.75
	<hr/> \$59,629.26

### BUDGET

BUDGET 1944		BUDGET 1945
\$3000	<b>Salaries:</b>	\$3000
3000	Secretary .....	4000
2000	Executive Secretary .....	2000
	Treasurer and Assistant Treasurer .....	
500	<b>Expenses of Officers and Delegates:</b>	
	President .....	800
2350	President-Elect .....	200
2000	Secretary .....	3800
0	Treasurer .....	2500
0	Executive Secretary .....	500
700	Supervising censors .....	0
200	Delegates to the House of Delegates (A.M.A.) .....	700
350	Shattuck Lecture .....	200
	Cotting Luncheons .....	400
	General administrative expenses under supervision of President and Secretary .....	2000
200	<b>Committees Elected by District Societies:</b>	
100	Executive .....	400
200	Legislation .....	3200
0	Public Relations .....	300
	Nominations .....	0
200	<b>Standing Committees:</b>	
	Arrangements:	
115	Estimated income .....	\$11,335.75
25	Estimated profit .....	\$3,361.95
1500	Ethics and Discipline .....	200
0	Finance .....	25
100	Medical Defense .....	1500
6750	Medical Education .....	0
	Membership .....	100
	Society Headquarters —	
	Regular .....	3700
	Extra .....	1200
13,000	Publications:	
200	<i>New England Journal of Medicine</i> .....	8000
25	Directory and miscellaneous .....	1600
200	Public Health .....	200
	Industrial Health .....	200

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ROY J. WARD, *Chairman*  
ERNEST M. MORRIS, *Secretary*

## APPENDIX NO. 5

### REPORT OF THE COMMITTEE ON SOCIETY HEADQUARTERS

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A second meeting of this committee was held on October 25, at 1:15 p.m. There were present Drs. Tighe, Ober and Reardon of the committee and also Drs. R. N. Nye, R. M. Smith, F. C. Hall and Eliot Hubbard and Mr. R. St. B. Boyd. In the absence of the chairman, Dr. Blaisdell, Dr. Ober called the meeting to order. Dr. Nye explained that the purpose of the meeting was to consider the item in the budget labeled "Headquarters." The money in this item although spent was never approved by any committee, which is required by the by-laws. It was explained that the chairman of the committee, Dr. Blaisdell, thought this ought to be a function of the Committee on Society Headquarters. Under this budget would be included miscellaneous items, clerical assistance for various committees and so forth. It was ex-



Medical Society shall report to the Council of the Massachusetts Medical Society that this committee is in favor of finding and expanding common grounds of agreement with representative groups of the public and that a committee be appointed by the President with the end in mind of creating a general understanding of the problems involved in good medical care.

After general discussion in the committee the following motion was unanimously passed, namely, that, recognizing our obligation to further the education of the public in regard to medicine, it be recommended to the Council that the President appoint a special committee, containing representatives of the Committee on Public Relations, Committee on Ethics and Discipline, Committee on Publications, Committee on Public Health and any others that he desires to further the education of the public in regard to medical questions, particularly through popular magazines.

Three questions about industrial-accident cases were referred to the subcommittee on Industrial Accidents, headed by Dr. Ellison. These questions were: the abuse of the rules that an injured employee may have the services of a physician of his own choice; a question of the correct charge by a doctor to a patient whom he treated, the case having previously been declined by the Committee on Ethics and Discipline; and the question of simplified insurance forms, which was brought to the attention of the committee by the Norfolk District Medical Society.

The report of the meeting attended by representatives of the New England Roentgen Ray Society, the chairman of the Section of Radiology of the Massachusetts Medical Society and the Committee Appointed to Confer with the Massachusetts Hospital Association was read and discussed by the Committee on Public Relations. The committee approves the principles laid down by the above-mentioned groups. These principles will be outlined in the report furnished by Dr. Phippen, chairman of the Committee Appointed to Confer with the Massachusetts Hospital Association.

ALBERT A. HORNOR, *Secretary*

## APPENDIX NO. 8

### REPORT OF THE SUBCOMMITTEE TO MEET WITH THE MEDICAL ADVISORY COMMITTEE OF THE STATE INDUSTRIAL ACCIDENT BOARD

This subcommittee was originally appointed to meet with the Advisory Committee of the State Industrial Accident Board but at the last meeting of the Committee on Public Relations, the subcommittee was asked to take up three problems directly with the Board itself.

The first concerns a complaint in writing against an alleged practice of insurers and employers of compelling an injured employee to submit to treatment by the surgeon and at the hospital designated by them. Many surgeons say that when employees request their services rather than those of the company-appointed man that the employee faces discharge or at best unpleasant treatment thereafter by the employer. The chairman of the State Industrial Accident Board authorizes the subcommittee to say that if any doctor who has had such an experience or who knows of such a case will present all the facts in writing to her, including the date of the accident, the name of the employee and of the foreman, nurse or other that in any way shows this illegal action toward an injured employee, she will take prompt action to stop such practices.

The second problem was concerned with a matter of ethics and procedure that is becoming increasingly serious to the Industrial Accident Board. An employee developed an inguinal hernia, responsibility for which was denied by the insurance company. He then contracted to have the hernia operated by a private physician to whom he agreed to pay \$250, this amount to include hospital and operation fees. Subsequently the Industrial Accident Board found for the employee, and he felt that the insurer should pay the entire \$250. Your subcommittee thought, and this opinion was endorsed by the chairman of the Industrial Accident Board, that the insurer should pay only the amount usually allowed by the Board for the surgeon and hospital in an uncomplicated case of this type.

This matter of industrial accidents is not a one-way street. One of the great problems now facing the State Board is a practice that is becoming widespread, especially in Boston. An employee has an abdominal pain and calls a physician, who examines him, makes a diagnosis of hernia, says the operation must be done at once, sends the sick man into some private nonapproved hospital and operates. These hospitals keep very sketchy records. There is no proof available whether the patient had a hernia or, believe it or not, whether a herniotomy was done. The Board does not want to penalize an honest workman who has a real hernia; on the other hand it does not intend to encourage this practice. Your subcommittee recommends that a committee from the Society be appointed to study this problem and report at some future time to this Council.

The third problem was in the form of a suggestion from the Norfolk District Medical Society that industrial accident forms be shortened. We should appreciate this district society's presenting us with a form that it considers adequate. It would seem rather difficult to do this, as most certainly there must be a name, an address, a date, a history, a physical examination, a relation of the cause and effect, a report of laboratory findings, including x-ray, a report of the number of visits, a statement of complications and a prognosis. On submission of a short form, however, your subcommittee will be happy to go back to the Board with it.

As chairman of this subcommittee for the past two years, I want to pay tribute again to Mrs. Emma Tousant, chairman of the State Industrial Accident Board. This woman has the interest of all parties at heart—the insurer, the employee and the doctor. She is as nearly impartial and just in her decisions as any human being can be. I consider her one of the outstanding women in public life in this state.

DANIEL J. ELLISON, *Chairman*

## APPENDIX NO. 9

### REPORT OF COMMITTEE ON POSTWAR PLANNING

The Committee on Postwar Planning held its first meeting on November 8, 1944. It was voted that subcommittees be appointed to deal with certain subjects and that a secretary of the committee be appointed by the chairman. Dr. L. E. Parkins agreed to serve as secretary.

The Subcommittee on Hospitals, under the chairmanship of Dr. Nathaniel Faxon, will consider the changing place of hospitals in medicine and in the community, the need for providing additional internships and residencies and the opportunity for responding to the greatly increased public interest in hospitals.

The Subcommittee on Postgraduate Education, under the chairmanship of Dr. W. R. Ohler, will study the field of postgraduate education, not merely in hospital centers but in regions at a distance from medical schools.

The Subcommittee on Medical Schools, under the chairmanship of Dr. Charles F. Branch, will report the influence of the changing curriculums in medical schools, particularly the part played by medical schools in the postgraduate education of the future.

The Subcommittee on Organization, under the chairmanship of Dr. Chester M. Jones, will consider means of increasing the services that the Society renders to its members and also the relation of the Society to other organizations within the community, both lay and professional.

The Subcommittee on Economics, under the chairmanship of Dr. L. S. McKittrick, will study the changing economic relations of medicine, particularly in the fields of prepayment insurance and of contract medicine and the probable place of private practice in the changing economic order.

A second meeting of the committee was held on January 24. The committee believes that the interest of each community in Massachusetts in the general problem of public health is now greater than ever before. Many women as well as men have given volunteer service to hospitals and medical and public-health institutions, and coming for the first time in direct contact with modern medicine, they appreciate its promise. It is common knowledge that during the war years medical students have been hurried through an accelerated medical course, have experienced short internships and have often been placed on active duty as medical officers in positions where they have had little opportunity to acquire ex-



Special Committees:			
25	Cancer .....	0	80.00
0	Physical Therapy .....	50	
25	Postgraduate Instruction .....	25	79.09
0	Expert Testimony .....	50	
0	Automobile Insurance Claims (committee discharged)		150.00
150	Prepayment Medical-Care Costs Insurance (Committee discharged)		429.76
0	Tax-Supported Medical Care .....	50	102.83
0	To Meet With Massachusetts Hospital Association .....	50	\$682.59
0	Maternal Welfare .....	50	
100	Rehabilitation .....	50	124.91
550	Postpayment Medical Care .....	200	98.09
750	Military Postgraduate .....	1000	
800	War Participation .....	600	
300	Postwar Loan Fund .....	0	
300	Conference to Discuss Wagner Bill (committee discharged)		\$223.00
2500	Bureau of Clinical Information .....	2800	273.60
0	Postwar Planning .....	3000	
10	Medical Advisory to Regional OPA .....	10	104.00
0	Better Publicity for Massachusetts Medical Society .....	100	105.00
4000	Refund to district societies .....	4000	208.24
			92.15
\$46,225		\$52,960	\$782.99
			30.00

### DETAILED EXPENSE ACCOUNTS

ESTIMATED EXPENDITURES 1944	ESTIMATED EXPENDITURES 1945	\$80.08
<b>President:</b>		
Miscellaneous .....	\$200	
Clerical work .....	200	
Flowers to funeral .....		
Luncheons .....		
Postage .....		
Telephone .....		
Travel .....		
<b>Secretary:</b>		
Clerical work .....	1800	
Postage and mailing .....	500	
Printing .....	1100	
Stenographic reports of Council meetings .....	200	
Miscellaneous .....	140	
Telephone .....	60	
<b>Treasurer:</b>		
Clerical .....	500	
Investment counsel (Loomis and Sayles) .....	1000	
Excess clerical expense (N. E. J. of Med.) .....	318	
Billheads and printing .....	185	
Miscellaneous for balance of year .....	97	
Hartshorn and Walter (public accountants) .....	400	
<b>Executive Committee:</b>		
Clerical work .....	200	
Dinners .....	100	
Ballots for referendum Postwar Loan Fund .....		
Miscellaneous .....	100	
<b>Committee on Public Relations:</b>		
Clerical work .....	75	
Dinners .....	175	
Miscellaneous .....	50	
<b>Committee on Arrangements:</b>		
Hotel .....	5986	
Printing .....	428	
Returned rentals .....	340	
Clerical work .....	207	
Guest speakers .....	123	
Motion pictures .....	153	
Rental of scientific booths .....	120	
Publicity .....	138	
Signs .....	162	
Miscellaneous .....	343	
Estimate for balance of year .....		
<b>Committee on Ethics and Discipline:</b>		
Clerical work .....	100	
Luncheons .....	60	
Miscellaneous .....	35	
Postage and mailing .....	5	
<b>Committee on Public Health:</b>		
Clerical help and postage .....	200	
<b>Committee on Medical Defense:</b>		
Counsel fees .....	1500	

<i>Committee on Membership:</i>		
Clerical and committee meetings	100	
<i>Committee on Industrial Health:</i>		
Stenographic service, postage, dinner meetings	200	
<i>Military Postgraduate Committee:</i>		
Dinners	250	
Clerical	350	
Miscellaneous	200	
		\$1000
<i>War Participation Committee:</i>		
Dinners		
Miscellaneous	100	
Clerical	300	
Committee meetings	100	
Postage, telephone, stationery	100	
		\$600
<i>Bureau of Clinical Information:</i>		
Secretary	1820	
Telephone	200	
Printing and postage	500	
Typewriter	115	
Additional electricity	100	
Miscellaneous	65	
Furniture		
		\$2800
<i>Committee on Postwar Planning:</i>		
Dinner	1500	
Stenographic service	500	
Postage, telephone, stationery		
Miscellaneous	1000	
		\$3000

*New England Journal of Medicine*

	ACTUAL 1944*	ESTIMATED 1945
Revenue:		
Advertising .....	\$39,000	\$45,000
Engraving .....	1,000	1,500
Reprints .....	4,800	4,000
Subscriptions .....	54,000	60,000
Miscellaneous .....	1,200	1,500
	<hr/> \$100,000	<hr/> \$112,000
Expense:		
Publication of <i>Journal</i> .....	\$65,000	\$70,000
Publication of reprints .....	6,100	3,500
Office and other salaries .....	25,200	27,000
Commissions, fees, etc. ....	7,200	7,500
Office and sundry expenses .....	6,500	7,000
	<hr/> \$110,000	<hr/> \$115,000
	100,000	112,000
	<hr/>	<hr/>
Loss .....	\$10,000	\$3,000
Appropriation .....	\$13,000	\$8,000

\*Based on ten months' operation.

## APPENDIX NO. 7

## REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

The committee has studied the question of policy in supplying advice to lay inquirers coming into a community about the selection of a family physician. The committee recommends that all requests for information by the laity, as to whom they should consult, should be referred to the secretary of the respective district society.

The Subcommittee on Publicity reported to the Committee on Public Relations, and their report was unanimously adopted. Important features of this report were as follows: it was the unanimous vote of the subcommittee that in view of the probability of not getting an ideal man now we should not try to hire a publicity agent at the present time; meantime, the secretary of the Society should instruct and encourage the executive secretary of the Society to familiarize himself with medical publicity; it was the unanimous opinion of the subcommittee that the expense of the work suggested in the above recommendation should be charged to administration; and it was the unanimous opinion of the subcommittee that the publicity of the annual meeting is the responsibility of the Committee on Arrangements. The Committee on Public Relations recommends the adoption of these principles.

After prolonged discussion it was duly moved and seconded and the following motion carried unanimously, namely, that the Committee on Public Relations of the Massachusetts

that such a fund will enable the Society to assist certain members or the families of members who have served the Nation during these trying days and members in the future who may be faced at any time with unexpected financial vicissitudes. (Its establishment at the present moment will make of it an expression of appreciation by the Society to those of our members who served with the armed forces during the present war.)

GEORGE LEONARD SCHADT, *Chairman*

## APPENDIX NO. 11

### REPORT OF THE COMMITTEE ON MATERNAL WELFARE

Dr. R. S. Titus presided at a meeting held October 26, 1944, at which the following members were present: Drs. R. M. Smith, T. Almy, R. L. DeNormandie, W. R. Sisson, J. M. Baty, Florence L. McKay, R. P. Moulton and E. S. Bagnall.

Dr. Smith asked if the Society should aid in distributing information concerning the EMIC Program. Dr. Bagnall discussed this and stated that he felt it was unfortunate that the Society and doctors in certain communities were so antagonistic to the program.

The question was brought up concerning how many members of the Society were participating in the EMIC program. It was thought that the Massachusetts Medical Society should do more to publicize the service which the EMIC program offered. Attention was called to the fact that physicians have not read the available literature released by the Department of Public Health.

It was brought to the committee's attention that supplemental fees are said to be demanded by physicians in some cases before they would agree to take cases under the EMIC Program. Before further discussion on this subject, a motion was made by Dr. Smith, that the secretary send a letter to Dr. Florence L. McKay, director of the Division of Child Hygiene of the Massachusetts Department of Public Health, calling her attention to the fact that physicians were said to be collecting a fee for obstetric service under the EMIC Program after mothers had requested such service but before the applications were signed by the phy-

sician and requesting that Dr. McKay furnish any facts that she may have concerning this report.

It was the sentiment of the committee that further investigation of maternal deaths be held in abeyance at this time.

A motion was made that a subcommittee be appointed for the purpose of keeping themselves informed about the activities of the EMIC Program and making necessary recommendations with the co-operation of the Massachusetts Department of Public Health.

A survey of the prenatal program was discussed.

The direction given to the secretary of the committee in the fourth paragraph of this report brought forth the following answer:

November 21, 1944

Dear Dr. Sisson:

In reply to your letter of November 10, 1944, I would say that we have received verbal information that some physicians are charging mothers a fee before they sign the application for Emergency Maternity and Infant Care. This has been reported to me by two different physicians who came to the office to discuss the matter, by agencies, and by the mothers themselves. We have nothing whatever in writing. In some cases names have been given, and in one, a physician informed Dr. Saunders, during a telephone conversation, that it was his custom to do this.

We would appreciate any action which the Massachusetts Medical Society might wish to take to improve the situation and to bring about a better understanding with the attending physician as to the purpose of the Emergency Maternity and Infant Care Program.

Sincerely yours,

(Signed)

FLORENCE L. MCKAY, M.D.  
Director, Division of Child Hygiene

Following the meeting, Dr. Bagnall and Dr. Titus appointed the following subcommittee: Dr. Ralph E. Cole, chairman, Dr. Benjamin Lambert and Dr. Daniel J. Ellison. Letters have been sent to these men, notifying them of their appointment to the committee.

WARREN R. SISSON, *Secretary*

perience useful to a civilian medical practice. By necessity they will need opportunities for further preparation before commencing their professional civilian careers. On the whole, a unique opportunity is close at hand for medicine in Massachusetts to increase its service in a variety of ways.

At the meeting of the Council on June 9, 1936, certain recommendations by the Subcommittee on the Adequacy of Medical Care of the Committee on Public Relations were duly adopted by vote. These recommendations were as follows:

I That each district society be urged to form, within its area, medical service councils composed of carefully chosen representatives of its own membership, representatives of welfare agencies, hospital boards, health and welfare departments, nursing and dental societies and the general public. The functions of these councils to be:

1 Education of the public in the needs and possibilities of medical service, preventive as well as curative, and in the ways available for securing it.

2 Making provision for suitable clinics or district visiting services where need is found (rural and factory village areas).

3 Securing co-operation in its program from industrial, fraternal, social and health organizations.

4 Establishing welfare department responsibility for and intelligent administration of medical care for the indigent and near-indigent in each town and city by:

a Employing the licensed physicians of the community at reasonable pro rata fees.

b Subsidizing licensed practitioners to locate where there are no resident physicians.

5 Influencing established hospitals to broaden their function so as to serve as health centers in co-operation with local health departments and as welfare centers in co-operation with local welfare departments.

6 Promulgating, locally organizing, and thereafter serving as an advisory body in the administration of any programs of voluntary insurance for hospitalization and medical care which may receive the approval of the State Society.

II That a state medical service council of similar constitution be developed whose functions shall be to co-ordinate the work of the local councils, advise as to methods, study legal relations and devise enabling statutes when necessary to simplify procedures and increase efficiency in carrying out the primary purpose of promoting better health by bringing adequate medical care to the people and relieving economic distresses which are detrimental thereto.

At present twenty-three local health councils are in existence, co-operating with the Central Health Council. Although physicians have been members of such councils, the fellows of this Society have not taken such an active interest in their proceedings as is desirable. This committee believes that they should be activated and that additional councils should be organized.

The chairman suggests that the Council authorize the President to inform the president and secretary of each district society, the chairman of each health council, the superintendent or chairman of the staff and the chairman of the board of trustees of each hospital in the Commonwealth whose staff members are in community practice concerning the following resolution:

RESOLVED, That the Council of the Massachusetts Medical Society, having in mind the unusual problems of medical care to be presented now and in the postwar period, recommends (1) the formation of health councils where none exist, or where the present council is inactive, to be composed of physicians and dentists, hospital trustees, public-health specialists, educators, editors, employers and representatives of labor and groups concerned with the distribution of medical care, to consider and adopt further measures for extending medical services in the community and increasing preventive-health education both by local effort and through co-operation with state and federal bodies, (2) more active participation by physicians

in the work of health councils already in active existence, and (3) that the Committee on Public Relations implement these recommendations in such manner as the committee deems most profitable.

HOWARD F. ROOT, M.D., Chairman

## APPENDIX NO 10

### REPORT OF THE POSTWAR LOAN FUND COMMITTEE

The Postwar Loan Fund Committee approves in principle the desirability of raising funds from which loans can be made to members of the Massachusetts Medical Society who, having served in the Armed Forces, may be in need of immediate financial assistance on discharge from active duty.

The committee makes the following recommendations:

1 That the Council of the Massachusetts Medical Society authorize the establishment of a postwar loan fund.

2 That the Postwar Loan Fund be established by an assessment of \$10.00 for the current year, the amount of any subsequent assessment, if any, to be determined by the Council at its annual meeting.

3 That payment of the Postwar Loan Fund assessment by members of the Massachusetts Medical Society while in the armed forces be entirely optional.

4 That those members who have been in the armed services, together with nonresident members, be exempt from the assessment if they request it, and that those members who are ill, aged or in difficult financial circumstances be exempt if they have the approval of the Committee on Membership for such exemption.

5 That the amount of loan granted be left to the discretion of the board or committee appointed by the President, that just enough interest be charged — not to exceed 2% — to cover carrying charges and remind the member obtaining a loan of his obligation, and that no endorsers be required.

6 That loans shall be limited to a period of twelve months, subject to renewal at the discretion of the board or committee appointed.

7 That only those who were members, in good standing, of the Massachusetts Medical Society on the date they entered the armed forces shall be permitted to borrow from this fund.

8 That to inform members of the Society in the armed forces of the availability of this fund, information be printed in the *New England Journal of Medicine*. There shall also appear in a box on the cover of the *Journal* an announcement calling attention of the members to the article on the inside page, that form letters shall be sent to the members in the armed forces, notifying them of the existence of this fund, and that form letters shall be sent out to the other members of the Society with the annual bills for dues bringing to their attention the existence of this fund and its purpose.

9 That the Postwar Loan Fund be supervised by the Massachusetts Medical Society and not by the district medical societies.

10 That the president of the Massachusetts Medical Society appoint a committee or board of five members, to include the treasurer and the secretary of the Society, and the present chairman of the Postwar Loan Fund Committee, to administer this fund.

11 That the immediate purpose of the proposed Postwar Loan Fund of the Massachusetts Medical Society is to establish a fund which shall make available financial assistance to such members of the Society who, on discharge from active service as medical officers in the present war, may need temporary financial aid, that the fund will become a permanent fund of the Society, the income or principal to be used from time to time for the purpose of assisting members or families of members of the Society who may be in need of temporary financial aid (the fund will be administered by a committee elected each year by the Council on nomination by the President),

that such a fund will enable the Society to assist certain members or the families of members who have served the Nation during these trying days and members in the future who may be faced at any time with unexpected financial vicissitudes. (Its establishment at the present moment will make of it an expression of appreciation by the Society to those of our members who served with the armed forces during the present war.)

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WARREN R. SISSON, *Secretary*

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*\*

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 31201

#### PRESENTATION OF CASE

A thirty-eight-year-old janitor was admitted to the hospital because of progressive dyspnea.

About four weeks before entry he developed a sore throat, hoarseness, a cough productive of thick phlegm, definite swelling of the legs, dyspnea and orthopnea. The dyspnea was most marked on exercise and when lying in bed. During the three to four weeks before entry he had slept fitfully and used three pillows. He thought that he had lost about 30 pounds in the six to eight preceding weeks.

He had had no chest pain, palpitation, nausea or vomiting. He had had nocturia (two times) during the two nights before entry. Sometimes, especially recently, the urine had been quite cloudy.

He had had measles and mumps but had not had scarlet fever. At the age of nine he had had chorea and swelling of the legs for over a month. Repeated epistaxis but no fever, rash, pains or sore joints accompanied this illness. He recovered completely and had not been susceptible to upper respiratory infections until the present illness except that on two occasions in the past few years he had had an episode of "grippe," accompanied by back and leg pains, which lasted about a week. He had worked at many jobs, having been in the Army at approximately the age of eighteen. He had had frequent physical examinations, the last one having been made four months before admission, and at none of these was he told that he had a heart murmur. Thirteen months before admission his blood pressure was 140 systolic, 92 diastolic. He had never before been hospitalized. About one and a half years before entry he traumatized his left testis, which had since become large. He smoked one package of cigarettes a day and drank an occasional glass of beer and little coffee.

Physical examination revealed a moderately well nourished, well developed, pale, ill appearing, orthopneic man. The teeth were decayed. There was marked pitting edema of the entire lower half of the body, extending up to the scapula. The right chest was clear, and over the left posteriorly were heard numerous musical and crackling rales. The

heart sounds were regular, and there was a Grade I apical systolic murmur. In the left scrotum was a large, firm, nontender mass measuring 25 by 10 by 10 cm. The prostate was slightly tender and somewhat enlarged.

The temperature was 100°F., the pulse 112, and the respirations 20. The blood pressure was 180 systolic, 115 diastolic.

The urine was cloudy, amber and acid in reaction, with a specific gravity of 1.024, and gave a +++ test for albumin; the sediment contained innumerable white cells and many red cells and hyaline, granular and cellular casts. Examination of the blood showed a white-cell count of 10,400, with 59 per cent neutrophils, 23 per cent large lymphocytes and 12 per cent small lymphocytes. The red-cell count was 3,300,000, with 10.8 gm. of hemoglobin. The stool was formed and brown and showed a +++ guaiac test. The corrected sedimentation rate was 1.4 mm. per minute. A blood Hinton test was negative, and tuberculin tests in dilutions of 1:10,000 and 1:100,000 were negative in forty-eight hours. The serum nonprotein nitrogen was 61.0 mg. per 100 cc., and the protein 5.08 gm., with an albumin-globulin ratio of 0.97. The cholesterol was 185 mg. per 100 cc. A cephalin flocculation test was negative in forty-eight hours. Urine cultures showed a few colon-bacillus colonies and a rare colony of a nonhemolytic streptococcus. A phenol-sulfonephthalein test showed 15 per cent excretion in the first fifteen minutes and a total of 67 per cent at the end of two hours. An electrocardiogram showed normal rhythm at a rate of 90, a PR interval of 0.16 second and sagging ST segments in Leads 1, 2 and CF<sub>1</sub>. The T waves in Leads 1, 2, CF<sub>1</sub> and CF<sub>2</sub> were inverted; those in Leads 3 and CF<sub>3</sub> were low and upright. The ST segment in Lead 3 was slightly elevated. The patient was digitalized with Cedilanid shortly after admission.

X-ray examination of the chest showed no distinct outline of the heart, owing to density in the adjoining lung fields. The vascular markings appeared to indicate diffuse engorgement, and there were widespread areas of increased density in both lungs, particularly in the lower portions. There was a small amount of fluid in both pleural cavities. Following an intravenous pyelogram, there was poor concentration of dye, and definite evidence of impairment of kidney function bilaterally; there appeared to be some fluid in the abdomen.

The temperature was approximately normal until the seventh day, when, immediately after the intravenous pyelogram, there were chills and fever; the temperature was 105°F. for thirty-six hours and then returned abruptly to normal. The white-cell count during the fever was 22,000. The pulse was paradoxical at a rate of 150 for a brief period, and the respirations 40. The urine contained enormous numbers of red cells, along with the white cells and casts, and still gave a +++ test for albumin. There

was slight tenderness in the costovertebral angles, which was more pronounced on the left than on the right. With digitalis and ammonium chloride the edema disappeared and the patient lost about 15 pounds. An x-ray examination of the chest on the eighth day showed most of the increased density of the right lung to have cleared, a small amount persisting in the right costophrenic angle. The left lower lobe had decreased markedly in size, but there was still considerable density within it. The total twenty-four-hour protein loss in the urine was 13.6 gm.

On the tenth day, although the patient was not dyspneic or uncomfortable, the serum nonprotein nitrogen was 110 mg. per 100 cc., the carbon dioxide 5.4 millimols per liter, and the chloride 107 milliequiv. The acid phosphatase was 1.7 Bodansky units per 100 cc., the alkaline phosphatase 5.4 units, the phosphorus 3.8 mg. and the calcium 7.6 mg. Ammonium chloride was stopped, and the carbon dioxide promptly began to rise.

The temperature, pulse and respirations after the ninth day remained approximately normal.

After two weeks in the hospital, the urinary output fell from 1500 to about 1000 cc. and the non-protein nitrogen and albumin-globulin ratio improved somewhat. A repeat chest film three weeks after admission showed almost no change. Dental x-ray films revealed multiple carious teeth, apical abscesses and retained root fragments. During the third and fourth weeks, the chemical determinations and the patient's appearance and well-being showed definite improvement, the carbon dioxide reaching 15.3 millimols per liter; the urine remained unchanged.

Shortly after receiving a whole blood transfusion the patient went to the bathroom, where, apparently without straining, he turned ashen gray and became dyspneic. Loud gurgling rales were heard, and within five minutes he expired.

#### DIFFERENTIAL DIAGNOSIS

DR. JACOB LERMAN: In summary, we have a thirty-eight-year-old man who came in with an acute respiratory infection associated with congestive failure. The weight loss of 30 pounds is puzzling, for in congestive failure there should be a gain in weight. One must assume some underlying process in addition to congestive failure.

The past history suggests a rheumatic type of infection without any residual. He is known to have had good health except for one blood pressure reading of 140 systolic, 92 diastolic, which has to be considered as borderline. He had had trauma to the left testicle, which resulted in a mass about 10 cm. long. Examination showed an orthopneic, dyspneic man with extensive edema, obvious congestion of both lungs and some underlying disease in the lungs. I should like to hear from the roentgenologist whether or not there was evidence of underlying

infection. The urine was consistent with acute nephritis. He had a moderate anemia, a rapid sedimentation rate and negative Hinton and tuberculin tests. He had some evidence of impairment of renal function, a low serum protein and reversal of the albumin-globulin ratio, probably owing to albumin loss. I should interpret the electrocardiographic changes as being due to left ventricular strain and digitalis effect rather than to coronary disease.

He had a rather uneventful course in the hospital for the first three or four weeks except for the episodes of fever following the injection of diodrast and the residual changes in the lungs as indicated by x-ray examination. Perhaps we should look at the films now.

DR. MILFORD D. SCHULZ: The heart is enlarged but without characteristic configuration. Some fluid is present in both pleural sinuses, and there are some patches of airless lung in both bases that obscure the heart shadow. In a week this process is seen to have subsided, but there is still fluid in the right pleural sinus. Then a week later another patch of airless lung has appeared at the left base, with the evidence of fluid no longer present.

DR. LERMAN: The record states that the left lung was diminished in size.

DR. SCHULZ: Yes; the left hilum is depressed, and the left lower lobe is reduced in size.

At the time the excretory urograms were made the dye was eliminated by the kidneys in such poor concentration that nothing can be said about the morphology of the calyces and pelves. The outlines of the kidneys can be made out; they seem to be normal.

DR. ALLAN M. BUTLER: Are not the shadows of the kidneys large?

DR. SCHULZ: Perhaps they are slightly enlarged. I still think that they are probably within normal limits.

DR. LERMAN: Do you still see evidence of collapse in this last film or does the lung appear normal?

DR. SCHULZ: I cannot tell.

DR. LERMAN: Apparently there are three groups of signs and symptoms to be considered: cardiorenal, pulmonary and those of the mass in the testicle. Everything in the story seems to be consistent with a diagnosis of acute glomerulonephritis following a respiratory infection. There is nothing in the history or physical examination to suggest that the patient had a previous underlying chronic glomerulonephritis. Acute glomerulonephritis explains the hypertension, the acute cardiac failure, the extensive edema and the urinary changes.

The nephrotic stage of chronic glomerulonephritis has to be considered. As I have already said, there is no evidence of chronic glomerulonephritis. In any case, it explains only part of the picture, and one would have to assume an acute process on top of the chronic. The same is true for acute pyelonephritis. Here one finds that white cells predominate

jerks were less active on the right than on the left; both ankle jerks were absent; the plantar response was extensor on the right, and flexor on the left. Sensory examination was unsatisfactory; at times there seemed to be some impairment of the sense of passive movement, but there was always some doubt about this.

The temperature was 98°F., the pulse 80, and the respirations 20. The blood pressure was 110 systolic, 78 diastolic.

Examination of the blood showed 4,040,000 red cells, with 12.2 gm. of hemoglobin, and a white-cell count of 8100. The urine gave a + test for albumin; the sediment contained 25 white cells, a few epithelial cells and rare red blood cells per high-power field, as well as calcium oxalate crystals. The blood sugar was 96 mg. per 100 cc., and the nonprotein nitrogen 34 mg. A blood Hinton test was negative. Lumbar puncture revealed an initial pressure equivalent to 210 mm. of water; there were no cells, the protein was 44 mg. per 100 cc., the colloidal-gold reaction was normal, and the Wassermann reaction was negative.

X-ray examination revealed normal lung fields and a calcified tortuous aorta. In the skull there was an area of greatly increased density, measuring 7 by 7 by 2 cm., in the right anteroparietal region. This was sharply defined and appeared to lie against the inner table. No pineal shadow was visualized. The posterior clinoid processes were somewhat decalcified.

An electroencephalogram was reported as grossly abnormal, showing high-voltage, slow-wave activity throughout but most pronounced in the left postfrontal region. Examination by the cortical testing laboratory seemed to indicate that former intelligence had been normal and that defects had developed, particularly inability to think out a problem, choice of words, reading ability and memory.

After about two weeks there was some return of motion of the right leg, and following that, slight voluntary motion of the right arm and hand. The right foot remained paralyzed. There was never any spasticity. On the twenty-seventh hospital day the patient had a convulsive seizure. She first lost consciousness and then had convulsive movements of the left arm and leg lasting one minute. She was unconscious about five minutes and was incontinent of urine and feces. The findings following the seizure were essentially unchanged. After this there was no further improvement, the right arm and hand even becoming a little weaker. There was never any headache. Just before discharge, five weeks after entry, the senses of position, passive movement and two-point discrimination were found to be impaired.

*Second admission* (two months later). The patient had improved for a time and was eventually able to walk a few steps. Then the paralysis gradually

became worse, and beginning a few days before entry, she rapidly lost ability to talk. There had not been any headache.

Physical examination revealed a wide-awake and fairly alert patient. She obviously recognized her former doctors and understood at least a part of what was said to her. All that she could say was "yes" and "no," and these words were not always used appropriately. There was a right hemiplegia, with marked weakness of the face and complete paralysis of the arm and leg.

The temperature was 100°F., the pulse 90, and the respirations 20. The blood pressure was 95 systolic, 70 diastolic.

The urine showed a + test for albumin, and the sediment contained 15 white cells per high-power field. Examination of the blood showed a white-cell count of 9200, with a hemoglobin of 14.3 gm. The nonprotein nitrogen was 22 mg. per 100 cc.

On the ninth day after admission the patient became less responsive and in the late afternoon was found unconscious and covered with vomitus. Shortly after that she "stiffened out," with the head retracted and the respirations deep and noisy. The left arm was rigid and extended, and the right arm was partly flexed as before. The eyes were directed straight forward, and there were fine nystagmoid movements of the left eye. The pupils were 2 mm. in diameter, equal and fixed to light. After a short time the left arm relaxed. The arm and knee jerks were present and equal. There was no plantar response on either side. The patient remained in deep coma and died eight hours later, the temperature rising to 102.5°F. before death.

#### DIFFERENTIAL DIAGNOSIS

DR. MANDEL E. COHEN: The history of this illness covers six months from the first symptom to death. The first three months showed paralysis and weakness, first of the right leg and then the right arm, and finally definite hemiplegia, aphasia and confusion. The patient was studied in the hospital for over a month. During that time she showed slight confusion and had one convulsion. Apparently she improved somewhat and went home. In a couple of months she became progressively worse, particularly with regard to the right hemiplegia and aphasia. She was readmitted to the hospital and within a week went into coma and died. In other words, we have an illness of six months' duration, with a fairly steady progression of symptoms, except for a slight, short remission.

In considering a case of this kind, we should ask ourselves, What are the facts? Where is the lesion? What is the diagnosis? One has to emphasize the first question somewhat because, unfortunately, the instrument with which the patient gives the facts, namely, the brain, is diseased, so that sometimes the information may be misleading or even unobtainable.

"About a week before admission to the hospital she became confused and had difficulty in saying what she wanted to say, not being totally aphasic." At this point I should like to know just what "confused" meant. This word is used to describe a variety of symptoms. It may mean that a patient cannot find the right word to express himself but has nothing wrong with his understanding; it may also mean that a patient may not be able to enunciate clearly or understand the spoken language. These different disabilities may all be called "confusion." Some of these details are important in the localization of a lesion. This patient had had no headaches or at least complained of no headaches. In thinking about the possibility of brain tumor that has to be seriously considered.

At the time of the second admission the reflexes were less active on the right than on the left, and both ankle jerks were absent. Then there was some impairment of the sense of passive movement, but it does not say on which side.

DR. CHARLES S. KUBIK: It was on the weak side.

DR. COHEN: X-ray films of the skull showed something on the right side that was said to be sharply defined and to lie against the inner table of the skull, the posterior clinoids being somewhat decalcified. The location of the increased density immediately introduces a great difficulty, because the hemiplegia was on the right side. The patient was aphasic, and although we are not told, she was presumably right-handed, so that we should naturally look for a lesion on the left side. We are told, however, that there was a large calcified lesion, which was 7 by 7 by 2 cm., on the right side of the skull.

I think we must accept it as a fact that the patient had a right hemiplegia; that, in addition to the aphasia, was the main disability and should be the basis of our localization.

Do we know whether she was right-handed?

DR. KUBIK: I believe that she was.

DR. COHEN: Let us assume that she was right-handed. Occasionally one can be misled in lateralizing lesions from handedness since about 5 per cent of right-handed people have their speech centers on the right.

DR. KUBIK: The hemiplegia was on the right side too.

DR. COHEN: The most reasonable supposition is that she had a right hemiplegia and aphasia. The

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convulsion that was observed, most of the motor movements were on the left side. What does a convulsion tell us about localization? If the seizure is observed from the beginning and if there are unilateral movements, it is good betting that the lesion is on the opposite side. There are some other points, however, that should be mentioned. Sometimes a convulsion lasts an extremely short time. The crucial observation may be made by a student nurse or an untrained attendant who rushes in, and in the excitement, rights and lefts may be mixed up. A second possibility is that the fit may start on one side, but by the time it is observed, the only movements discernible are on the nonaffected side, the affected side having developed paresis. Another possibility is that in a patient who has a hemiplegia one sometimes observes that that paralyzed part does not enter into the convulsion. I had the opportunity once to observe a young man in another clinic who was diagnosed hysteria. He had a hemiplegia, and one physician thought a good cure for this would be to give an electric shock. This was given and his fit was observed only on one side of the body, that is, the paralyzed side did not convulse.

We have two bits of evidence to make us wonder about a lesion on the other side—the x-ray films and the fit on the wrong side. This brings up the possibility of two lesions or of one very extensive one.

Terminally the patient went into coma; the neck was retracted, and she developed the type of phenomenon which is evidence of what might be called decerebration. There are two possible explanations of that. One is that the patient had a mass with increased intracranial pressure and eventually suffered from herniation of the brain stem, with coma, pupillary abnormality and death. The other and less likely explanation is that the patient had intraventricular hemorrhage with blood in the third ventricle. We sometimes see this identical phenomenon in a patient with subarachnoid hemorrhage. Most of the evidence points to the fact that the lesion that gave the patient the most trouble was on the left side and was mainly frontal, although the function of the parietal area was also affected.

What was the nature of the lesion? One must consider various diagnoses here because certainly this is not an open-and-shut case, and even when a case seems to be clear cut it sometimes turns out not to be. The first consideration is a mass of some kind; the second, vascular disease, and then syphilis; and finally one should also include degenerative disease, such as Alzheimer's disease.

In favor of a mass of some kind, particularly a brain tumor, is the course of this illness. It was slowly progressive, with but slight remission. The march seemed rather steady and slow, which is in all likelihood the progress of a brain tumor. If this was a brain tumor, was it metastatic or primary?



There is no evidence of any primary source for a metastatic lesion. The patient apparently was in good health, had not lost weight and had no symptoms that pointed to any system of the body. So if she had a secondary neoplasm we are not able to diagnose it from the evidence. To be sure she had slight albumin and a few white cells in the urine, but she had no significant urinary symptoms to incriminate the kidney as a primary source for the tumor.

Could the mass have been of some nature other than neoplastic? Could she have had an intracranial hematoma, or two intracranial hematomas? She had had an injury fifteen years previously. As you know, everyone has injuries at some time or other, and in the evaluation of a case injury always comes in, sometimes as a red herring. If hematomas, they were quite chronic subdural hematomas; it is barely possible that the mass on the opposite side was an old calcified subdural hematoma. May we get an expression from the X-ray Department at this time?

DR. MILFORD D. SCHULZ: This is the area of increased density, which is continuous with the inner table of the right side of the skull; it apparently straddles the frontoparietal suture. It is homogeneous in density and thins out at the edges to meet the normal bone. It did not change during the three-month period of observation. The only thing that seems to have happened during this interval is that the posterior clinoid processes are not so well seen on the last examination as on the first. There are a lot of diploic channels in the parietal bones, particularly on the left side, but I think they are still within the bounds of what may be seen in normal people.

DR. COHEN: There are more channels on the left than on the right. They come to no special focus?

DR. SCHULZ: They are more prominent on the left, but they certainly can also be seen on the right side.

DR. COHEN: Can you tell by stereoscopic examination whether the mass is outside the dura, inside the dura or in the brain?

DR. SCHULZ: No, because you cannot see the dura. The dense mass is probably outside the dura, however, by reason of the fact that it seems to be continuous with the inner table; there is nothing in between it and the parietal bone.

DR. COHEN: The x-ray films do not help us a great deal in arriving at a diagnosis. It is possible that they may lead us away from the answer.

The second possibility is that this was vascular disease of the brain. In any patient sixty-two years old there is always the possibility of cerebral thromboses. The course, however, seems too gradual, and the method of death, probably by herniation of the brain stem, is not the proper one for cerebral thromboses. The spinal-fluid pressure was only slightly elevated, which could be consistent with this idea;

however, even a slight increase, if reliably measured, points to the tumor.

Syphilis would be unusual. It can cause the slow progression of hemiplegia and also convulsions. The patient had no serologic or other evidence of syphilis, and if she had syphilis we cannot diagnose it.

Against Alzheimer's disease or Pick's disease, both of which may give hemiplegia and fits, is the fact that the local manifestations were more pronounced than the general psychologic difficulties. Pick's disease has, however, been described as giving quite localized symptoms at the onset. These rare disorders are only remote possibilities.

The reason it is necessary to mention all the other possibilities is that this patient, a brain-tumor suspect, lacked headache, choked disks and obviously increased spinal-fluid pressure—the three characteristic signs of brain tumor. She apparently had no choked disks in the first examination. We are not told about the second time. The spinal-fluid pressure was not particularly elevated. She had no headaches. About 90 per cent of people with brain tumor have headache. Patients with aphasia may not be able to tell about headache or may forget to tell; nevertheless, lack of headache is a serious difficulty in diagnosis.

Another question that we must consider since we see a mass by x-ray on the opposite side from our suspected lesion is, What diseases give bilateral intracranial lesions?

Perhaps she had multiple lesions or one extensive lesion covering both sides of the brain. Of course, this mass may have been unrelated to her symptoms. But how could it have been related to the lesion? Subdural hematomas are frequently bilateral and sometimes do calcify. Brain tumors, particularly meningiomas, neurofibromas and angiomas, may be bilateral and also may calcify. Parasagittal meningiomas that grow to such an extent that they are visible on both sides of the head have been described, so one could include this possibility in the diagnosis. But we cannot say really what is on the other side of the head by x-ray.

We are left with the bare facts that this patient developed hemiplegia and aphasia over a six-month period and died. It is on these unequivocal facts that we must rest our case. Most of the findings indicate that the patient had a left-sided lesion. Putting all the evidence together the best bet is that the patient had a brain tumor of some kind. Glioma is the most frequent brain tumor, and it is proper to pick that on the basis of probability. A diagnosis of meningioma, however, would include the possibility of bilateral lesions, which is the most reasonable way to explain the left-sided lesion and the right-sided mass.

DR. W. JASON MIXTER: I think it is only fair to say that when I saw this patient I had the same feeling that Dr. Cohen had. It seemed to me that there was x-ray evidence of an extensive lesion on the

right side, with symptoms suggesting a tumor on the left side.

DR. KUBIK: The patient herself was opposed to having anything done at the time of the first entry, and because she had improved slightly, she wanted to go home for a while. At the time of the second entry, while we were wondering what to do, being reluctant, because of the aphasia and apparently conflicting findings, to do anything at all, the patient rapidly got worse and in the course of about twenty-four hours died. The clinical diagnosis on the death report was brain tumor, and that was also the diagnosis made at the time of the first entry.

#### CLINICAL DIAGNOSIS

Brain tumor.

#### DR. COHEN'S DIAGNOSES

Brain tumor, left frontal region: bilateral meningioma or glioma.  
Herniation of brain stem and cerebellum.

#### ANATOMICAL DIAGNOSES

Meningioma: left parietal region.  
Osteoma of skull, right.  
Pressure cones, cerebral and cerebellar.  
Cerebral infarction: left occipital lobe and cerebellum.

DR. KUBIK: At post-mortem examination the left hemisphere was considerably larger than the right. On the right side there was a depression, made by the bony mass that was seen in the x-ray films. That was solid bone, about 2.0 or 2.5 cm. thick, apparently an osteoma. There was every common variety of pressure cone, each one marked. A large part of the medial surface of the left cerebral hemisphere had herniated beneath the falx, and there was a large left temporal pressure cone, as well as a cerebellar pressure cone. Associated with the left temporal pressure cone there was hemorrhagic infarction of the medial portion of the left occipital lobe, including the calcarine cortex. This has been observed a number of times with temporal pressure cones. As the medial portion of the temporal lobe is forced into the notch of the tentorium the posterior cerebral artery is compressed against the inner free edge of the tentorium, and that presumably is responsible for the infarction. In this case there was also infarction of the superior surface of the cerebellum over the distribution of the left superior cerebellar artery. There was a firm, discrete tumor 3 cm. in diameter in the left upper parietal region, and an enormous amount of swelling of the white matter of almost the entire left cerebral hemisphere. Although such swelling of the brain occurs regularly with brain tumor, it was unusually marked for the size of the tumor in this case. It is quite possible that diminution in the size of the cranial cavity by the osteoma intensified the pressure effects. The tumor was a meningioma.

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## EPIDEMIOLOGY OF WOUND INFECTIONS

As in all infectious diseases the epidemiology of wound infections involves many factors that concern the host, that is, the patient and his wound, on the one hand and the invading organisms on the other. Some of the reservoirs from which these organisms arise and the importance of their recognition in the prevention of serious wound infections have recently been reviewed in a lecture by A. A. Miles,\* professor of bacteriology at the University of London, who has made notable contributions in this field. What he has to say about these infections

is equally applicable to war wounds and to surgical wounds in civilian life.

Alexander Fleming, now widely known as the discoverer of penicillin, is given credit for the first complete bacteriologic history of an infected war wound. He distinguished three phases: the first, which is characterized by a dark, reddish-brown, foul-smelling, watery discharge, lasts about a week; the second, during which the discharge becomes less copious and more purulent, lasts another week or so; and the final stage, which is one of pyogenic infection, lasts for a varying length of time. In the first stage, spore-bearing and gram-negative bacilli predominate. These are replaced during the second stage by pyogenic cocci, which persist and flourish. Similar descriptions, with some variations, have been given by numerous other writers since that time.

In a study of wounds in men from Dunkirk and in air-raid victims, Miles found that indifferent cocci, spore-bearing bacilli and coliform organisms appeared early and were gradually replaced by pyogenic cocci, mostly *Staphylococcus aureus* and hemolytic streptococci, and other coliform bacilli. The original contaminants behaved like saprophytes, since the majority seemed to be killed by the tissues of the host. Because of the possibility of accurately identifying the late-appearing hemolytic streptococci by grouping and typing, these were selected as the best organisms to follow in tracing the origin of wound infections.

Such infections may arise from two sources, namely, the injury and its environment. Surgeons, on the whole, hold to the opinion that the organisms are implanted at the time the wound is sustained and that they become clinically and bacteriologically predominant later. They therefore place the chief emphasis on operative technics, débridement and cleansing procedures and the use of sulfonamides and penicillin locally and systemically to prevent their multiplication and spread. Bacteriologists, on the other hand, consider that most of the late-appearing organisms are usually added after the infliction of the wound. The distinction is important, for if the former is correct, then the entire attention must focus on the early treatment of the wound; whereas if the latter is true, then "the whole life of the wound must be our concern."

\*Miles, A. A. Epidemiology of wound infections *Lancet* 1 809-813, 1944

Miles considers two main reservoirs of hemolytic streptococci—one the open lesions of patients with streptococcal wound infection, pharyngitis, scarlet fever or puerperal fever and the other the throats and, to a lesser extent, the noses of healthy carriers. From these sources there arise contaminations of the dust, clothing and bedclothes, which in turn may cause infection both of the cases and of the carriers from which the organisms arise and of those around them.

Recent evidence indicates the chief reservoirs of virulent staphylococci to be not the skin, as previously thought by most workers, but rather the anterior part of the nasal cavity. From 30 to 70 per cent of persons can usually be found to carry *Staphylococcus aureus* in the nose, whereas only 5 to 20 per cent are skin carriers. Significantly enough, most of the skin carriers are also nasal carriers. In addition, the staphylococcus-carrier state is usually a permanent rather than a transient one. Throat carriers of pathogenic staphylococci are infrequent.

Another highly important feature of staphylococcal infections is their dependence on personal contact and not on environmental factors. Staphylococci are not usually found in large numbers in the air even in a ward in which there are many patients whose wounds are infected by them. Streptococci, on the other hand, are broadcast from the throat through droplets during talking, coughing and sneezing. Since staphylococci are rare in the throat, they are spread by droplets only during occasional sneezing. The real broadcasters of staphylococci are the hands, which have innumerable opportunities of becoming contaminated with them. As compared to streptococci, the potentially pathogenic staphylococci seem to be much more dependent on actual contact for access to wounds, but the latter organisms are also much more widely distributed among human carriers, all of whom carry them in large numbers.

Silent infections, that is, the presence of streptococci or staphylococci in clinically clean wounds, both large and small, constitute another significant reservoir of infection. This is true both in civilian and in military practice. Such silent infections may be as frequent or even more frequent than clinical

infections, and they are mostly staphylococcal. The infecting organisms are often added after infliction of the wound, and their presence has been shown definitely to prolong the healing time. Epidemiologically, these silent infections may be of even greater danger than the manifest ones because of the fact that they are unrecognized. A typical example is a small cut on the finger of the doctor or nurse, "which serves as an *entrepreneur* between the upper respiratory tract and the patient's wound and goes into production on its own."

The risks of infection from each of the reservoirs vary with the age of the wound. In this respect, Miles distinguishes three types of infection. The first, of course, is the infection of the wound that takes place at the time the injury is sustained. The second is self-infection from the upper respiratory tract and the skin, and its danger is continuous throughout the history of the wound. Miles has been able to show that the wounds of those who are staphylococcus carriers are likely to be contaminated with that organism at the time of injury. The third is infection in the hospital, which is considered to be the gravest, because of the concentration of the reservoirs of infection and of the susceptibles. It is there that wounds are exposed for dressings under conditions highly favorable for the transfer of infection unless they are done under operating-room conditions. Indeed, from 30 to 80 per cent of cases become infected on hospital wards.

The prevention of the infection that follows contamination at the time of injury is concerned with the "toilet of the wound" and the use of prophylactic antibacterial agents, such as sulfonamides and penicillin. By means of the former, the bulk of the infected material is removed and the conditions for resistance against those that remain are improved. Dressings impermeable to bacteria then reduce the risk of infection from the outside, except during inspection and dressings.

The successful prevention of added infection depends on an appreciation of their source. These may be either air-borne or spread by contact, the latter probably being the more important except in the case of large wounds or burns. One must recognize that the danger from air-borne infection is greatest when dust is stirred up, particularly after

sweeping or bedmaking. It is also necessary to bear in mind that the ordinary procedure of changing a dressing is one of the methods by which a large number of pathogenic bacteria are discharged into the air. Recently the application of oily substances to the floors and bedclothes, to keep down the dust, has proved more effective in controlling infection than have methods of sterilizing the air.

The risks of contact infection are well recognized by surgeons. They do not, however, have the same respect for the open wound on the ward that they have for the clean incision made in the operating room. If both these types of wounds were given the same consideration, Miles believes that the danger of hospital infection of wounds would be almost completely eliminated. He cites instances in which an aseptic routine in handling wounds, with comparative neglect of the air-borne elements, resulted in a striking reduction in the rates of secondary streptococcal and staphylococcal infection. In one clinic, for example, streptococcal infections were reduced from 31 to 2 per cent in this manner.

Surgeons in these busy days are apt to be rather careless in the manner in which they handle wounds and dressings. If the arguments presented by Professor Miles are correct, much time for both the surgeon and the patient would eventually be saved by the aseptic handling of wounds. This would obviously necessitate a considerable change in habits and procedures, but it seems likely that the added effort would be repaid by a reduction in the incidence of secondary wound infection and, hence, by an increase in the rapidity of healing.

MASSACHUSETTS MEDICAL SOCIETY  
COMMITTEE ON LEGISLATION

The following letter was sent on May 2 to all members of the Committee on Legislation.

WILLIAM E. BROWNE, *Chairman*  
\* \* \*

Dear Doctor:  
Realizing that your own district society is probably having a meeting in the near future, and that you might be called on for a report, I am sending you this letter to bring you up to date on legislative affairs.  
This session of the Legislature has taken final action on very few bills in which we are interested, although the hearings on most of these bills are finished.  
House 973, a bill that we favored, requiring corporations organized for the purpose of conducting medical schools

to file an annual return to the Secretary of State was finally enacted, being signed by the Governor on April 18.  
Senate 215 and House 762, bills either to abolish the Division of Occupational Hygiene or to transfer it from the Department of Labor and Industries to the Department of Public Health, were both given leave to withdraw.  
Senate 273, a bill relative to the practice of medicine by hospital interns, fellows or medical officers, was rewritten as House 1672, passed and signed by the Governor on April 4.  
Senate 54, a bill requiring physicians and surgeons to furnish written statements in certain cases, was given leave to withdraw on February 26; we opposed this bill.  
Senate 69, a bill to establish a board of registration in chiropractic, was rewritten as House 1738 and given to the Ways and Means Committee. We plan to oppose it again when it comes up for a hearing.  
The three osteopathic bills are House 1394 and Senate 396 and 397. The first bill was withdrawn, but the last two were heard before the Committee on Education early in April. These bills would allow the Board of Registration in Medicine to accept the certificate of the National Board of Examiners for Osteopathic Physicians, just as they now accept the certificate of the National Board of Medical Examiners.  
All the following bills, House 754, 755, 858, 859, 860, 1014 and 1396 and Senate 422, were proposed by adherents of either Middlesex University College of Medicine or the College of Physicians and Surgeons to break down the present Approving Authority law. They try to do this by repealing the law, postponing its effective date or making exceptions to it. The proponents of these bills talked for five days before the Committee on Public Health and for two days before the Committee on Education. We answered in two days and one day, respectively. Our side was ably upheld by Dr. H. C. Weiskotten, dean of Syracuse University College of Medicine and secretary of the Council on Medical Education and Hospitals of the American Medical Association, Dr. Lee, Dr. Bagnall, Dr. Mongan and others. What the recommendation of the committee will be, and when it will be announced, we do not know, but it behooves all of us to enlighten our representatives and senators on the true facts of the situation.  
Two more bills have been heard by the committees, but no report has yet been made public. These are Senate 421 and 446. The former bill proposes that, if any hospital accepts medical students, it must accept them from all legally chartered schools, and the latter would open every hospital to every physician.  
The members of the Committee on Public Health, before whom most of these bills have been heard, have been most patient. We have not tried to coerce anyone, but rather to aid them in arriving at their decisions.  
We shall probably have to ask you again to get in touch with your senators and representatives regarding these measures which affect the health of all the people of the Commonwealth.

WILLIAM E. BROWNE, *Chairman*  
Committee on Legislation

DEATHS

DUCKERING — William W. Duckering, M.D., of Dorchester, died May 3. He was in his eighty-fourth year.  
Dr. Duckering received his degree from Harvard Medical School in 1898. He was formerly on the staff of the Boston Dispensary. He had been retired from practice for seven years.  
Two sisters and a niece survive.  
KING — Nathaniel C. King, M.D., of Brockton, died January 23. He was in his eighty-fourth year.  
Dr. King received his degree from the College of Physicians and Surgeons, New York, in 1884.

MCCARTHY — Eugene A. McCarthy, M.D., of Bedford, died January 1. He was in his eighty-fifth year.  
Dr. McCarthy received his degree from Harvard Medical School in 1887.

OBER — Ralph B. Ober, M.D., of Springfield, died April 13 at Sarasota, Florida. He was in his sixty-sixth year.

Dr. Ober received his degree from Harvard Medical School in 1901. He served as a major in the Army Medical Corps during World War I. He was on the senior surgical staff at Springfield Hospital, having been president at one time. He was a fellow of the American Medical Association, a member of the Springfield Medical Club, New England Surgical Society and American College of Surgeons and a diplomate of the American Board of Surgery.

His widow, a son, a daughter and two sisters survive.

PORTER — Charles T. Porter, M.D., of Waltham, died April 19. He was in his fifty-seventh year.

Dr. Porter received his degree from the University of Virginia Department of Medicine in 1912. During World War I, he served with the Harvard hospital unit in France with the British Army. He specialized in otolaryngology, was lecturer on otology at the Harvard Medical School and was associated with the Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital, Waltham Hospital, Children's Hospital, Massachusetts Women's Hospital, Brooks Hospital, Cambridge Hospital and Faulkner Hospital. He was a consultant at the Concord Hospital and Robert B. Brigham Hospital. He was a fellow of the American College of Surgeons and the American Medical Association and a member of the American Academy of Ophthalmology and Oto-Laryngology, American Laryngological Association, American Laryngological, Rhinological and Otological Society, American Otological Society and New England Otological and Laryngological Society. He was a diplomate of the American Board of Otolaryngology.

He is survived by his widow and a daughter.

It may be Sunday evening and your cellar has run dry;

For a long and frosty drink is what you're wishin';  
Why, it's simple, for the druggist will replenish your supply,  
If you have a little note from your physician.

Suppose on Friday evening that your tank is running low  
For the most entrancing week-end expedition;  
The solution's very easy: to your ration board you go  
With a breezy little note from your physician.

After countless hours of headache, when your income tax is due,

Since you're ill, for time to pay you must petition,  
You're forgiven by the Bureau of Internal Revenue  
If you have a little note from your physician.

When, at the end, you're pleading with St. Peter at the Gate,  
After finishing with pride your earthly mission,  
Be quite certain, even then, you impatiently will wait  
For that final little note from your physician.

APREXIA ALGERA

## CORRESPONDENCE

### DEPRIVATION OF LICENSE

*To the Editor:* At a meeting of the Board of Registration in Medicine held April 11, after a hearing of the case of Dr. Harry B. Bernstein, 100 Boylston Street, Boston, the Board voted to suspend his license to practice medicine in the Commonwealth for three months because of gross misconduct in the practice of his profession as shown by deceit in causing false and misleading advertisements to be inserted in the newspapers.

H. QUIMBY GALLUPE, M.D., *Secretary*  
Board of Registration in Medicine

State House  
Boston

### TATOOING FOR IDENTIFICATION

A recent confidential report from the man in charge of displaced persons for the United Nations Relief Association in France, makes one sad to hear of the scores of children who carry no means of identification. It is almost impossible to know even their nationality, for some are too young to talk intelligently. Experiments, such as saying "Come here, dear" in various languages and showing motion pictures of certain countries, fail in many cases to help in finding even from what country the children come. Some permanent means of identification should be invented so that none of the children in the United States are lost. For soldiers, this would reinforce the identification tag. It would also be useful in the identification of people who are killed in accidents and of criminals whose source of birth is difficult to place.

To overcome the difficulty of identifying lost people it is suggested that when a birth is reported, a number should be returned to the parents within two weeks and that this number should be tattooed on the child during the first month of life. The number would probably have to start with a letter indicating the country of origin, and the first two numerals in the number could probably be used to indicate the subdivision of the country — in the United States, they might indicate a state. Various parts of the body could be used for tattooing, such as the buttocks, the lower back or the supra-pubic region.

If the above suggestion meets with any approval, the whole matter should be referred to the Children's Bureau in Washington, where the mechanics of numbering the children and deciding the location for tattooing could be worked out, as well as the steps involved in making this a law. If the idea is adopted, experts in tattooing should be trained so that this minor operation could be done in a cleanly fashion and with little discomfort to the baby.

It is to be hoped that many other countries besides the United States will adopt a similar plan of identification.

HILBERT F. DAY, M.D.

34 Kirkland Street  
Cambridge, Massachusetts

## MISCELLANY

### PASSANO FOUNDATION AWARD GIVEN TO DR. COHN

On May 16 in Baltimore, Dr. Edwin J. Cohn, professor of physical chemistry and head of the Department of Physical Chemistry, Harvard Medical School, was honored as the first recipient of the Passano Foundation Award, which carries with it an honorarium of \$5000. The foundation was established in 1944 by the Williams and Wilkins Company, of Baltimore, to aid the advancement of medical research, especially that bearing promise of clinical application. For the encouragement of such research the foundation has established the award as one of its activities. Dr. Cohn is distinguished for his work on the fractionation of blood. Beginning in 1919 with a study of blood and blood proteins, Dr. Cohn's research has progressed until it has yielded a spectacular group of five fractions of blood plasma, which hold untold promise of usefulness in medical science. Following the presentation of the award by Mr. Edward B. Passano, chairman of the Board of Directors, Williams and Wilkins Company, Dr. Cohn read a paper concerning the applications of his work on blood plasma to the field of clinical medicine.

### DOCTORS' LAMENT

In spite of all the freedoms that you're fighting for today,  
Whatever be your station or position,  
For 'most anything that's needed, for your work or for your play,  
You must have a little note from your physician.

Now if of creamery butter you're extravagantly fond  
And its lack you find impairing your nutrition,  
To your pleas the kindly grocer will most pleasantly respond,  
If you have a little note from your physician.

It is true that in the winter, when your living room is cold  
And the radiator never starts to hissin',  
Coal or oil will be provided for not quite its weight in gold,  
If you have a little note from your physician.

## BOOK REVIEWS

*The Trials and Triumphs of the Surgeon, and Other Literary Gems.* By J. Chalmers Da Costa, M.D., LL.D. Edited by Frederick E. Keller, M.D. 8°, cloth, 401 pp. Philadelphia: Dorrance and Company, 1944. \$5.00.

Twenty-one addresses and essays of the late Dr. J. C. Da Costa are here collected in book form under the editorship of his younger colleague, Dr. F. E. Keller. The subjects embrace topics in the history of medicine, controversial medical issues, such as vivisection, the medical education of women and polypharmacy, biographical sketches, eulogies and graduation addresses. As Da Costa once said, "During my nearly thirty years of membership in the medical profession, many truths have crystallized in my mind, some as apothegms, some as aphorisms, and some as epigrams"; of these he cites no less than fifty-four in the address before the Philadelphia County Medical Society that gives the title to the book. Charles Dickens must surely have been his literary idol, for he places his lance at rest and tilts against medical shams, hypocrisy, quackery, pretensions and fashions with true Dickensian satire and cynicism. Senior students will do well to expose themselves to these precepts, expressed and implied, and will enjoy the experience; middle-aged doctors will chuckle over and find relaxation in them; but it will be the thousands of his former students in anatomy and surgery at the Jefferson Medical College who will enjoy again listening to the old master, recalling the kindly and warmly sincere nature of the teacher whose words were often so caustic and devastating. To the younger of them will appear again the unconquerable spirit of the man who continued to teach from a wheeled chair, the victim of a painful and disabling disease. And no reader should miss the touching poetical tribute by a friend, beneath the frontispiece picture of Da Costa's desk.

*Operations of General Surgery.* By Thomas G. Orr, M.D. 4°, cloth, 723 pp., with 1396 illustrations. Philadelphia: W. B. Saunders Company, 1944. \$10.00.

Dr. Orr's purpose in preparing this book is best indicated by a sentence from his preface, "A clear visualization of the steps in an operation is many times more instructive than the descriptive text." Accordingly, he has borrowed from recent textbooks and from surgical monographs and current journals and has added original drawings to a total of nearly four thousand illustrations, a very large number of which occupy the entire page. The text is necessarily brief to be included in the total pagination, and consists of a short description of the anatomy of the region, of the indications for operation and of particular dangers and safeguards, together with a concise enumeration of the operative steps.

The first three chapters constitute an introduction on the subject of wound healing as affected by surgical technic, the treatment of fresh wounds and the indications for various kinds of sutures.

In subsequent chapters the critical reviewer sometimes finds himself not in agreement with the author's judgment of relative values. Interscapulothoracic amputation is dismissed with two small figures showing the skin incision with but twenty-five lines of descriptive text, whereas depressed nipple is accorded two illustrations with almost as much text. A whole page plate with figures of twenty-two varieties of skin incision for radical mastectomy and little or no expressed opinion concerning their respective value must be confusing to the uninitiated. The figures illustrating vascular ligations are inadequate in comparison with others, and this is particularly the case in pulmonary embolectomy. It seems out of proportion to devote sixteen illustrations, most of them full-page, to abdominal incisions. In general, the operations on the abdominal viscera are perhaps the most satisfactorily presented. It seems unfortunate that in picturing four methods of gastrostomy Dr. Orr expressed no opinion concerning their relative merits, and similarly one wishes to know his views about the exact indications and usefulness of posterior gastroenterostomy. In describing proximal temporary colostomy for obstruction one could wish that mention were made of the Miller-Abbott tube, which so often renders this unnecessary. The account of hernia is excellent. The discussion of neurosurgery is limited to fracture of the skull, decompression and the suture and transplantation of nerves. There is an excellent brief analysis of the status of the surgery

of the sympathetic system. In the endocrine system one is surprised at the inclusion of total thyroidectomy for heart disease and angina pectoris, — a procedure that has been largely discarded, — and one notes in the text that in the operation for carcinoma of the thyroid gland "no attempt should be made to preserve the recurrent nerve," whereas the excellent illustration on page 574 shows the nerve to have been carefully preserved. Congenital anomalies and the genitourinary and female reproductive systems are satisfactorily illustrated, but one notes with regret that while the author states that "radical abdominal panhysterectomy includes the complete removal of the uterus with the tubes and ovaries," the six plates and descriptive text indicate that the tubes and ovaries have been preserved. Such discrepancies in a textbook are unfortunate. It could hardly be otherwise than that illustrations from so many sources would be of uneven merit, but most of them are excellent. The value of many is somewhat impaired by the lack of adequate labeling of structures.

The exact place of this handsomely manufactured and expensive volume in the library of the beginner and of the older general surgeon seems to this reviewer somewhat doubtful. He wishes that it reflected more of Dr. Orr's great wisdom and personal experience. It is his opinion that in the serious preparation for the performance of an operation the reader will usually find it necessary to turn to the original monographs and textbooks, to which this volume may be found to be an excellent guide.

## BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Savill's System of Clinical Medicine: The diagnosis, prognosis and treatment of disease for students and practitioners.* Edited by E. C. Warner, M.D., F.R.C.P. Twelfth edition. 8°, cloth, 1168 pp., with 185 illustrations and 7 plates. Baltimore: Williams and Wilkins Company, 1944. \$9.00.

This twelfth edition of a standard English work has been thoroughly revised in the light of modern advances in the field of clinical medicine. So much has been rewritten that few pages have escaped alterations, and much new subject matter has been added throughout the text.

## NOTICES

## ANNOUNCEMENT

Dr. Mark F. Lesses announces the removal of his office from 375 Commonwealth Avenue to 371 Commonwealth Avenue, Boston.

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 24

## FRIDAY, MAY 25

\*9:00-10:00 a.m. Periarthritis Nodosa and Acute Disseminated Lupus from the X-ray Viewpoint. Dr. Merrill Sosman. Joseph H. Pratt Diagnostic Hospital.

\*9:00-10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Cardiovascular Syphilis. Dr. Charles Kelly. (Post-graduate clinic in dermatology and syphilology) Amphitheater, Mallory Building, Boston City Hospital.

## SATURDAY, MAY 26

\*10:00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

## MONDAY, MAY 28

\*12:00 m.-1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

(Notices continued on page xvii)

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## THE CIRCUS DISASTER AND THE HARTFORD HOSPITAL\*

DONALD B. WELLS, M.D.†

HARTFORD, CONNECTICUT

An emergency anticipated and prepared for ceases to be an emergency.

**I**N TERMS of sudden death and human suffering, the circus fire of July 6, 1944, is the worst disaster that has overtaken Hartford in the more than three hundred years of her history. In less than three minutes 125 human beings, more than half of them children under fourteen, were burned to death on the lot. One hundred and eighty-three others, of whom 150 were burned, were admitted to the various hospitals, where 43 subsequently died. Some concept of this terrible disaster can be brought to you today.

The Hartford Hospital crystallized from disaster. Ninety years ago, on March 2, 1854, a boiler blew up in the Fales and Gray Car Manufactory in Hartford, killing 19 persons and injuring 23. A coroner's jury promptly placed the blame on the carelessness of the engineer, sermons were preached on the disaster, public recriminations were openly indulged in, and a pamphlet was published and sold for the benefit of the dead and injured. Responsible citizens, however, discussed the need of preparing for a possible repetition of such a disaster, and in May, 1854, two months later, the Hartford Hospital was incorporated. From a modest beginning the hospital has grown during the last eighty-eight years to become the most heavily occupied community hospital in the United States. The physical plant became inadequate, and a new hospital was projected. In April, 1942, the citizens of Hartford pledged for the new Hartford Hospital the largest sum of money ever raised by public subscription for a hospital in the history of the world.

The most essential factor in disaster preparedness that the hospital can provide is adequate shelter for the victims. The first unit of the new Hartford Hospital, the South Building, was opened in July, 1942. Its first purpose is to serve maternity patients and their babies; but the first floor, designed to be used ultimately as an outpatient department,

is constantly maintained as a properly located, adequately protected, completely equipped Triage Room, where a considerable number of casualties of any type can be assembled and definitive treatment instituted in the event of civilian disaster. An adequate drive and ambulance entrance open directly into a large foyer, where are stacked sawhorses and standard stretchers. Immediately adjoining the foyer is the Triage Room, 60 by 40 feet. Here twenty beds are kept constantly made up. At either end are lockers containing all necessary emergency apparatus. The room is equipped with utility hoppers; oxygen is piped directly into it; there is central suction; heavy-duty rubber-covered electric cables with multiple-plug receptacles placed at frequent intervals lie on the floor. Down the corridor from the foyer are two air-conditioned emergency operating rooms with complete pressure-sterilizing equipment, ordinarily used as cystoscopic rooms. Here, and in the regular accident rooms, on the afternoon of the circus disaster, the casualties were admitted and received their initial morphine and plasma, laboratory determinations were made, wounds were dressed, and ultimately the patients were transferred to the wards as these were set up to receive them.

Next to shelter and morphine, the most essential therapeutic agent in civilian disaster casualties, as in war, is blood plasma. The supply must be immediately at hand in adequate quantity. There is no substitute for blood plasma in the treatment of severe burns. The community had recognized this, and on December 15, 1941, eight days after the attack on Pearl Harbor, a proposition for a Hartford County blood-plasma bank of sufficient size and available to all the seven hospitals in the county in the event of civilian disaster was proposed to the six local Red Cross chapters. Responsible citizens accepted the proposal, and the community responded with its blood and money until a cache of 2700 pints of frozen plasma was in storage at strategic points against unexpected sudden demands of civilian disaster. So far as is known, such a cache of blood plasma contributed and paid for by a community,

\*Presented at the annual meeting of the New England Surgical Society, Boston, September 20, 1944.

†Visiting surgeon, Hartford Hospital.



is absolutely unique. On the day of the circus fire, the blood-plasma bank paid a large dividend to the community that had had the forethought to set it up: nearly 28 gallons of plasma was injected into the veins of the victims — with only a single mild reaction. Furthermore, up to August 29, volunteers had given an additional 85 pints of whole blood to the victims at the Hartford Hospital. It is interesting to note that a large part of the plasma, blood and electrolyte given the burned patients in the hospital was introduced directly into the femoral veins. Three hundred and thirty-five recorded femoral punctures were done by the house staff during the first three weeks following the fire without an untoward incident — nor were any common femoral veins ligated. One patient, who had sixteen femoral punctures, developed a transient, benign thrombosis of the right deep epigastric vein. In no case was any vein cut down on.

As is true of nearly every other community hospital during this war, the Hartford Hospital is chronically handicapped by a shortage of trained professional personnel. But the hospital as well as the community had prepared for civilian disaster. Five hundred and eighty-five Red Cross nurses' aides had been trained and graduated since the first class was inaugurated in March, 1942. An organized group of volunteer business and professional men known as "medical aides" had been formed at the Hartford Hospital in July, 1942, to meet the crises that had developed because of the disappearance of paid orderlies into the military services and expanded war industries. So far as is known, this is the first group of such volunteer men in the country to train for this type of work. A few of these volunteers were on duty at the Hartford Hospital on the afternoon of July 6. But as the news spread, a trained community flocked to the Hartford Hospital. It came first and continuously in the uniform or dress of its own nurses, staff and employees; then, almost as the victims arrived, it appeared in every professional and volunteer category: as trained nurses, volunteers going to work on the burned cases; as Red Cross nurses' aides, 40 remaining at the Hartford Hospital and 95 being directed elsewhere for service; as male medical aides, 105 of whom reported, 30 being retained for work in the hospital and the remainder going elsewhere for emergency service; as the blue-smocked volunteers; as soldiers from Bradley Field; and as servicemen from the telephone company, who stood by all night.

Burns are a special assignment at the Hartford Hospital, and a majority of all burns routinely admitted come under the care of the Burn Committee. For the benefit of the interns on duty in the Accident Room, the Burn Committee has a typed-out plan for the definitive treatment of such burns as may be assigned to it. Within three minutes of the arrival of the first patient on the day of the disaster the director, in accordance with plans adopted by

the staff and executive committee more than two years previously, declared an "emergency," which automatically placed all the disaster burns on an equal economic level and under the sole professional care of the Burn Committee. As a result, every burn that came into the hospital on July 6 was uniformly treated. The committee's typed-out plan closely follows the so-called "unorthodox method" employed at the Massachusetts General Hospital at the time of the Cocoanut Grove Disaster: immediate intravenous morphine; intranasal oxygen, if necessary; clinical evaluation of impending shock and absolute priority treatment of existing shock with plasma in adequate quantity as determined by frequently repeated laboratory checks; no cleansing or débridement of the local injury; simple protective pressure dressings, using previously prepared sterilized vaseline strips overlaid with dry gauze carefully and smoothly applied; sheet wadding rather than mechanic's waste; and Ace bandages. Folded newspaper splints are applied to extremities, with a second Ace bandage fastened to the newspaper splints with multiple safety pins. Every patient was supposed to receive intravenous sodium sulfadiazine. Each adult received 2 gm. at once, and a majority of the children received 50 mg. per kilogram of estimated body weight. Sulfonamides were entirely discontinued thirty hours after the disaster, when the National Research Council generously made an outright gift to the hospital of 220,000,000 units of penicillin, thus making it available to every victim in adequate dosage not only for therapeutic use but for prophylactic protection against possible infection.

The Burn Committee comprised three surgeons, four physicians, a pediatrician, two pathologists and adjunct members in various specialties. The day has long since passed when any severely burned patient can be considered as adequately cared for when his wound has been covered by some favorite local dressing. It cannot be emphasized too strongly that during the first forty-eight hours burns are a problem in physiologic chemistry and psychiatry; the only necessary surgical procedure in severe diffuse burns is to protect the wounds from infection and further trauma. The recognition and adequate treatment of shock is the all-important therapeutic problem; and in terrible mass catastrophes such as the circus fire severe emotional shock is superimposed on surgical shock. With this in mind, careful social-service investigation was promptly instituted in every case, and psychiatric evaluation and treatment were undertaken in a number of cases.

Fifty-one burned patients are said to have arrived at the Hartford Hospital within thirty minutes. Without the large Triage Room, previously prepared supplies, a reserve cache of frozen plasma, trained volunteer emergency personnel and uniform professional handling, the hospital would have been swamped. In all, 86 living patients were

brought to the hospital. Of these, 19 were dressed in the Triage Room and discharged as ambulatory cases. A total of 67 injured patients were admitted to the hospital, 54 of them having burns. Fortunately, a large surgical ward was in process of being painted, an overflow obstetric ward in the new South Building was not in use, and it was possible to clear other patients from the annex of a third ward. This permitted all the burned cases to be segregated; it simplified medical and nursing care, facilitated laboratory procedures and controlled visitors.

Beginning on the day following the disaster, formal rounds were regularly made at 10 o'clock each morning. All interested physicians were invited. A number of nationally known consultants were invited to come to Hartford, and they added a great deal of interest to the problems presented and discussed on these rounds. The name and the date of the expected visit of each consultant was posted in the Staff Room, and on one day there were thirty-five physicians in the group on rounds. Without exception the patients seemed to appreciate these visits; it made them feel that everything possible was being done for their safety and comfort. Each member of the Burn Committee was expected to speak to every patient as the group passed through the ward, and each consultant was personally introduced.

From the very first, visitors were admitted to the burn wards. During the first fortnight the number of visitors to each patient was limited to two and the duration of the visit to ten minutes; later the number of visitors permitted each patient and the visiting hours were extended to correspond with those on other wards in the hospital. Patients in a critical condition could be seen by members of their immediate family at any time. All physicians, personnel and visitors entering the burn wards were masked, a blue-smocked volunteer being constantly on duty at the door of each ward to enforce the rule. It is the belief of the Burn Committee that no infection was introduced or spread by this free access of professional men and relatives to the victims of the disaster, and there is a definite impression that it did much to maintain a high morale. Not a single patient asked to leave the hospital to secure different professional care, the comfort of special nursing or the exclusiveness of private-room accommodations.

As is so often the case in catastrophes, the burns followed a definite pattern. The vast majority of those who reached the hospital alive were burned solely by hot air. The vertex of the head, the extensor surfaces of the hands and forearms, the lateral surfaces of the arms, the upper back and exposed portion of the legs were uniformly the most severely burned areas. As they came into the Triage Room the victims appeared far more severely burned than eventually proved to be the case. Several had first-

degree burns almost from head to foot. Shock was the outstanding feature as they came in and for the first forty-eight hours after admission. The burned patients were primarily medical cases exhibiting marked physiologic imbalance, which required the closest clinical and laboratory observation, followed by prompt, intelligent and adequate therapy. The immediate results proved the validity of this thesis: not a single burned patient died at the Hartford Hospital of burn shock — a commendable record.

Five days after the fire, at the request of the National Research Council, a group of 7 patients began to have their local wounds dressed with pyruvic acid, followed by succinic acid and early skin grafting. This group was placed under the sole direction of Dr. G. J. Connor, assistant professor of surgery at Yale University School of Medicine, who originated and developed the method. It was a most interesting study and undoubtedly will be the subject of a subsequent detailed report. The local wounds of all the other patients were treated by the standard method — a bland ointment, a massive immobilizing dressing and delayed skin grafting of third-degree areas. It is most difficult to distinguish between deep second-degree and third-degree burns during the first few days; and it was amazing how some of the burns believed at first to be of third degree filled in from little scattered viable islands of epithelium.

Three of the burned patients admitted to the Hartford Hospital died. Each came to autopsy. The first, a twenty-two-year-old woman, died fifty-nine hours after admission. The anatomic diagnoses were second-degree and third-degree burns (10 to 15 per cent of total body surface), acute membranous laryngitis and tracheitis, pulmonary emphysema (bilateral), pulmonary edema (bilateral), diabetes mellitus and tracheotomy. The second, a thirty-five-year-old woman, died six days after the fire. The anatomic diagnosis was extensive second-degree and third-degree burns (50 to 60 per cent of total body surface). The third, a sixty-five-year-old woman, died twenty-eight days after the fire. The anatomic diagnoses were extensive second-degree and third-degree burns (50 to 60 per cent of total body surface), cellulitis, left lower extremity (anaerobic *Streptococcus haemolyticus*), thrombophlebitis, left femoral vein, and operative wound (split-graft donor sites).

\* \* \*

The circus fire as observed at the Hartford Hospital demonstrates that possible civilian disaster requires thoughtful preparation and specific organization on the part of the community, a hospital with adequate physical equipment and trained personnel and, most important of all, an organized professional staff with a clear concept of peripheral vascular failure and the significance of laboratory data, of infection and the limitations of bacterio-

atic agents, of nutrition, of the underlying principles of wound healing and of realistic psychiatry.  
 3 Asylum Street

### DISCUSSION

DR. CHARLES C. LUND, Boston: I want to compliment Dr. Wells on a perfectly marvelous job. I was one of those who had the good fortune to visit Hartford, not immediately, but about two weeks afterward, and saw the fine layout and at extremely fine work was being done.

I feel strongly, from the experience in Boston and that Hartford, that every hospital should have typed out and ready a disaster plan, and that this plan should include a plan to administer the care of burns, and probably a different plan to supervise the care of certain other kinds of disasters. How do we know that this morning we may not receive in the hospitals in Boston 200, 300 or 400 patients with any number of complicated fractures, from a train wreck right outside of, say, Readville, perhaps without any burns at all? These things are happening all the time. Owing to Civilian Defense, of course, there are such plans, but very few of them approach the one that Dr. Wells created and had ready in Hartford.

Supposing a disaster strikes, and one is faced with a problem of overloading. What should be done then? The Hartford Hospital was prepared, had plenty of room and was not overloaded. The Massachusetts General Hospital two years ago was not overloaded. The Boston City Hospital two years ago came very close to being overloaded. One hospital in Hartford, in my humble opinion, was overloaded at the Hartford disaster—both in the number of patients and in the severity of the cases. A 170-bed hospital received 100 patients. Fortunately there were 100 vacant beds. The hospital had one intern, it had a part-time staff, the staff rallied around, and they went to work.

If a patient with a fractured skull, injured in the woods of northern New Hampshire, can be safely sent to Boston, it seems sensible for burn patients to be shipped promptly away from a hospital that has its load, and only after all other hospitals in the area have been put in the same position of load—should any further patients go to that hospital. This is a hard thing to do. There is a disaster and everything is in confusion, but the staff of a hospital should put a responsible person on the street, who, when the conditions reach a certain point, should see that incoming patients go somewhere else. Patients were transferred from this hospital to

the Hartford Hospital later, and that corrected some of this overloading.

DR. OLIVER COPE, Boston: I, too, had the opportunity of going several times to Hartford and to the Hartford Hospital. I cannot overemphasize the intelligent care given by the hospital staff. It was one of those fortunate eccentricities of Fate that the circus fire should have occurred so near a hospital so well prepared.

I wish that at least part of the instructions to interns that had been drawn up by the Hartford Hospital Burn Committee could be published. There were several things of interest in them, and they were one of the reasons for the prompt, efficient care. For example, there was a description of how to do a femoral-vein puncture; I do not know of such a good, direct, simple account anywhere in the literature.

Leaving the question of management and foresight, there are other things that have emerged from the handling of this disaster by the Hartford Hospital. Doubt has recently been raised concerning the value of plasma in the treatment of the severely burned patient. There have been references to the substitution of sodium lactate solution. Anyone who had the opportunity to follow the detailed laboratory observations carried out almost hourly could have no doubt about the value of plasma in the treatment of burn shock. The data were beautifully arranged chronologically on a laboratory sheet that had been prepared for such a catastrophe.

The importance of plasma and good shock therapy is shown in relation to kidney function and damage. I visited one of the other hospitals that was less fortunately prepared in many ways and reviewed the laboratory data there. This hospital also did an excellent job in gathering information and taking care of the patients once an adequate force had been gathered. But there was a distinct difference; plasma therapy was delayed, and less of it was used. The Hartford Hospital's therapy was prompt and immediate, as it should be, and one had to search among a great number of extensively burned patients for a nonprotein nitrogen level that was above normal. In contrast, where therapy was even only moderately delayed, the rise in nonprotein nitrogen presumably due to impaired blood flow to the kidney, was dramatic. There was a striking difference in the values at the two hospitals.

There are other points, such as the control of sepsis achieved, that deserve mention in the handling of the burned patients at the Hartford Hospital. I hope that the staff will gather its information and publish it, because it will be useful to everyone in the future.

# SALICYLISM ACCOMPANIED BY RESPIRATORY ALKALOSIS AND TOXIC ENCEPHALOPATHY\*

## Report of a Fatal Case

HENRY W. RYDER, M.D.,† MURTON SHAVER, M.D.,‡ AND EUGENE B. FERRIS, JR., M.D.§

CINCINNATI, OHIO

THE purpose of this article is to report a fatal case of salicylism. The case is of special interest for the following reasons: the drug was given in the usual doses, as determined by symptomatic effect; the course of intoxication was directly shown, by studies of the blood acid-base balance, to be a respiratory alkalosis; tetany and electrocardiographic changes were observed; and at autopsy diffuse toxic encephalopathy was found.

The pH, whole-blood carbon dioxide content and hematocrit determinations were made as follows: Ten cubic centimeters of arterial blood was drawn into a dry syringe and immediately expelled into the cup of a Leeds and Northrup glass electrode potentiometer (No. 7661-A1 assembly), and the pH was determined before clotting occurred. The accuracy of this method is considered to be within  $\pm 0.05$  pH.

Another 10 cc. of arterial blood was collected under oil in a chilled container with 10 mg. of dry potassium oxalate powder added. The whole-blood carbon dioxide content was directly determined by the manometric procedure of Van Slyke and Neill.<sup>1</sup> The hematocrit was determined in Wintrobe tubes after centrifuging for one hour at 3000 r.p.m. No correction was made for cell shrinkage with the anticoagulant.

## CASE REPORT

I. L. (No. 6961), a 16-year-old Negress weighing 80 pounds, had been observed in the Medical Clinic over a period of several years for attacks of pain in the right lower quadrant of the abdomen. On admission to the hospital on October 18, 1940, the symptoms and physical signs of acute rheumatic fever with pancarditis were present. Briefly, the point of maximal impulse was in the 5th interspace in the anterior axillary line. A booming mitral first sound with a blowing systolic murmur and a rumbling diastolic apical bruit were heard. At the base pulmonic second sound was accentuated and palpable. A friction rub was heard over the 3rd left interspace. A high-pitched early diastolic blow was heard along the left sternal border. The lungs were clear. There was no pulsus paradoxus or peripheral signs of aortic insufficiency. No signs of chorea could be elicited. The reflexes were active without clonus.

The red-cell count was 5,940,000 and the hemoglobin 15.4 gm. per 100 cc. The white-cell count was 15,700, with 75 per cent neutrophils, 11 per cent lymphocytes, 13 per cent monocytes and 1 per cent eosinophils. The platelets appeared normal in number. The erythrocyte sedimentation rate was 11 mm. per hour, and a blood Kahn test was negative. The

urine had a pH of 5.5 and a specific gravity of 1.010; it contained no albumin or acetone; microscopic examination was negative except for an occasional leukocyte. The stool was normal in appearance and negative for occult blood. The electrocardiogram showed a PR interval of 0.20 second and a heart rate of 120 per minute; there was no axis deviation or elevation of the ST segments.

Treatment consisted of bed rest, a soft diet and the administration of 1.3 gm. of sodium salicylate every 3 hours. After a total of 15 gm. had been given, the patient complained of ringing in the ears and nausea with emesis. Fifteen hours later, sodium salicylate was resumed in doses of 1 gm. every 4 hours. During this period — the 4th and 5th hospital days — the fever, pericardial friction rub and all subjective manifestations of the disease disappeared. The blood pressure was 100/60, and two white-cell counts were 8900 and 5250.

On the 6th hospital day, after a total of 26 gm. of sodium salicylate, or 0.7 gm. per kilogram, had been administered, the respirations were noted to be rapid and slightly labored. At noon, the salicylate medication was discontinued because of vomiting. The respirations soon became deep and labored. The patient was restless and tossed about the bed. The muscles were spastic and the reflexes hyperactive with sustained ankle clonus, and positive Trousseau and Chvostek signs appeared. The red-cell count was 5,520,000 and the hemoglobin 13.0 gm. The white-cell count was 6400, the hematocrit 36.5 per cent, the formol-gel test positive, and the sedimentation rate 43 mm. per hour. A specimen of catheterized urine was strongly alkaline, with no albumin, sugar, acetone or blood (benzidine test). The centrifuged specimen showed 10 white cells per high-power field and no red cells or casts. The blood urea nitrogen was 21 mg. per 100 cc. and the carbon dioxide combining power 13.0 millimols per liter (29.0 vol. per cent). At 4 p.m., 4 gm. of sodium bicarbonate was administered by mouth. By 5 p.m., the patient was unresponsive except to painful stimuli. She remained stuporous and continued to hyperventilate throughout the night.

On the 7th day, a lumbar puncture showed an initial pressure equivalent to 220 mm. of water, which fell to 150 mm. on removal of 12 cc. of clear fluid. The fluid contained 13 red cells per cubic millimeter. No leukocytes were seen. A Pandy test was negative. At that time the serum calcium was 10 mg. per 100 cc. and the inorganic phosphorus 4.2 mg.; the white-cell count was 8850, and the catheterized urine showed a pH of over 7.5. One hour after the lumbar puncture the pH of the arterial blood was 7.58, the carbon dioxide content of the whole blood 7.3 millimols per liter (16.4 vol. per cent), and the hematocrit 27 per cent. Three hours later the carbon dioxide content of the whole arterial blood was 6.7 millimols per liter (15.0 vol. per cent). From 1 to 10 p.m. the patient was given 2500 cc. of fluid intravenously containing approximately 25 gm. of sodium chloride, and at 10 p.m. was deeply stuporous. The pH of the urine was 5.5. Respirations were still rapid but shallower than before. The Trousseau and Chvostek signs were negative. Occasional twitches of various muscle groups were noted. The patient was put in a tent supplied with 95 per cent oxygen and 5 per cent carbon dioxide, where she remained until her death. During the night, in the next 7 hours, she was given a total of 0.20 gm. of morphine sulfate with the intent of depressing the respirations, without apparent effect. She was incontinent of large volumes of acid urine.

On the 8th day, the pH of the arterial blood was 7.39, the carbon dioxide content of the whole blood 11.8 millimols per liter (26.4 vol. per cent), and the hematocrit 25.4 per cent. There were rales at the bases of both lungs, and much frothy material was aspirated from the throat. The white-cell count rose to 15,750, and the temperature gradually increased (Fig. 1). Culture of a throat swab showed no pneumococci. Sixteen hundred cubic centimeters of 5 per cent glucose

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in normal saline solution and containing 2.5 gm. of sodium sulfapyridine was administered intravenously. Twelve hours later, or 66 hours after the hyperventilation was first noted, the pulse became gradually more rapid and feeble and respirations ceased.

The time relations of significant data are shown in Figure 1.

**Autopsy.** Autopsy was performed 6 hours post mortem. There was gross and microscopic evidence of active rheumatic heart disease with pancarditis, and aortic and mitral valvulitis with mitral stenosis. There was chronic passive congestion of the liver and spleen and toxic changes in all the viscera. The left kidney was absent.

The gross changes encountered in the examination of the brain were confined to patchy subarachnoid effusions of blood, with small perivascular hemorrhages in the region of the 3rd ventricle and occasionally in the inferior portions of the basal

around blood vessels in the distended perivascular spaces. The large nerve cells were markedly diminished in the globus pallidus, and a scattered gliosis was observed throughout the basal ganglions, under the ependyma of the lateral and 3rd ventricles and in patchy areas in the deeper cortex.

No organisms were observed with the bacterial stains.

The anatomical diagnoses were as follows: active rheumatic myocarditis; aortic and mitral valvulitis; pericarditis; mitral stenosis; and nonspecific toxic encephalopathy.

#### COMMENT

Quincke<sup>2</sup> in 1882 reviewed the fatal cases of salicylate poisoning following its introduction into medi-

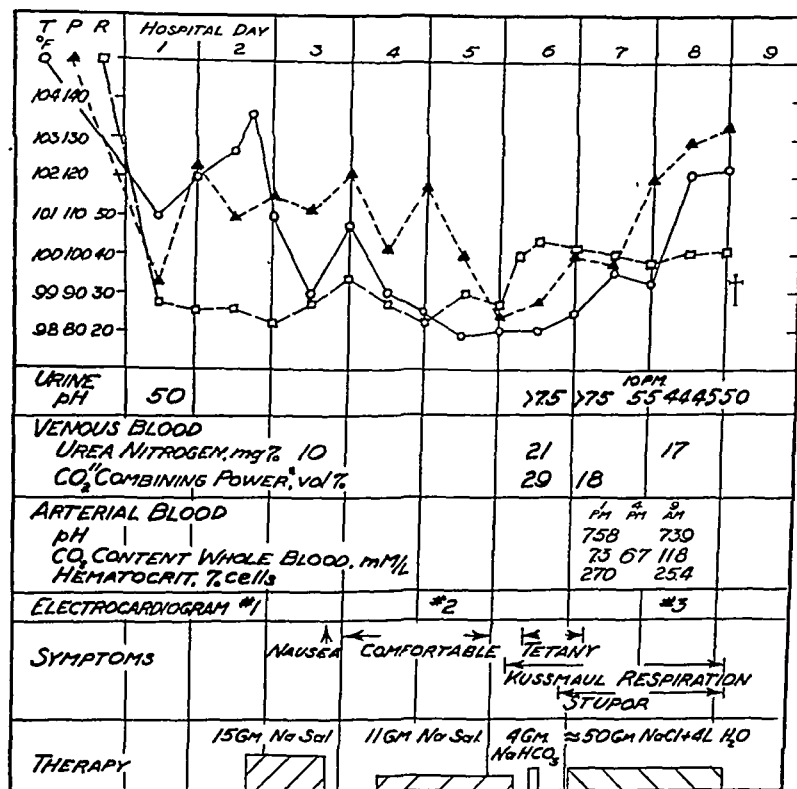


FIGURE 1. Time Relations of Significant Data.

ganglions. Congestion was observed throughout the basal ganglions, substantia nigra and pons and in the floor of the 4th ventricle.

Microscopic examination revealed a generalized swelling and slight chromatolysis of all the nerve cells in the cortex, basal ganglions and brain stem, associated with areas of severe nerve-cell degeneration, scattered particularly in the pyramidal layers of the cortex, basal ganglions and substantia nigra, and to a lesser degree in the nuclear masses of the brain stem. Small perivascular areas of early rarefaction were observed in the deeper layers of the cortex and in the basal ganglions. Hemorrhage and nerve-cell degeneration were most marked in the paraventricular nuclei and in the region of the 3rd ventricle. Many small vessels there and in the cortex contained hyaline thrombi, and in patchy areas in this region, as well as in the basal ganglions and brain stem, the capillaries exhibited moderate endothelial hyperplasia and were generally increased in numbers. The microglia was also increased in many of these areas, and the oligodendroglial cells were swollen throughout and markedly increased in the subcortical white matter and internal capsule. Satellitosis was marked in some areas of the cortex and basal ganglions, with aggregations of these cells

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addition the increased calculated pH of the arterial blood, even though there was no detectable clinical change in the breathing with the given doses of 5 to 6 gm. Odin<sup>6</sup> and Dodd, Minot and Arena<sup>7</sup> gave excellent discussions of the problem and made similar observations. They each reported several cases of clinical intoxication, although these cases do not conclusively demonstrate the presence of a respiratory alkalosis because of secondary compensatory factors. We have found no complete reports of the course of the acid-base changes in poisoned patients, but Guest and Rapoport<sup>3</sup> have noted an increase

The magnitude of these changes resulting from hyperventilation is striking, since the literature reveals no such low values attributable to a primary respiratory alkalosis. Equivalent changes in the carbon dioxide tension have, however, frequently been recorded in salicylate intoxication. In this case, partial correction of the abnormal acid-base balance following administration of saline solution and a return of the blood pH to normal value were not associated with any detectable improvement in the clinical condition.

In view of the finding at autopsy of a diffuse toxic encephalopathy, it appears that the hyperventilation, which was central in origin, and death were related to the encephalopathy. Whether this encephalopathy was caused by the toxic effects of salicylate or by the rheumatic process itself cannot be directly proved, but there is considerable evidence that salicylism was the cause of the acute changes. The onset of the fatal symptoms occurred following the administration of rather large doses of salicylate and during a period when the rheumatic manifestations had completely subsided. Although the dose of salicylate was within the usual therapeutic range, it was definitely above the mean toxic dose for women, according to Hanzlik.<sup>9</sup> Toxic and fatal manifestations with both larger and smaller doses than were given this patient have been described.<sup>5, 10</sup> Furthermore, this patient exhibited the classic symptoms of salicylate intoxication, namely, severe hyperpnea and a low carbon dioxide tension of the blood; also, the brain changes in this case are similar to those of the few autopsied cases reported in the literature.<sup>11</sup> Since the patient was suffering from subsiding rheumatic fever, it is, of course, possible that the encephalopathy was a part of the rheumatic process. This was the interpretation of Dobbs and de Saram<sup>12</sup> in their report of a patient who followed a very similar course. The encephalopathy of rheumatic fever has recently been studied by Winkelman and Eckel<sup>13</sup> and by Alpers.<sup>14</sup> Pathologic changes in the brain of the type seen here were reported in 1922 in a case of rheumatic fever by Greenfield and Wolfsohn,<sup>15</sup> who briefly discussed the literature up to that time. Hyperpnea was extreme in their case, but they do not state whether the patient was receiving salicylate.

Apparently the differential diagnosis of chorea, rheumatic encephalopathy and salicylate encephalopathy cannot be made through a morphologic investigation. In this case, however, the time relations of the course of the acute rheumatic fever and the salicylate therapy, the clinical rarity of severe encephalopathy as a complication of acute rheumatic fever and its apparent — although largely unrecognized — frequency as the end stage of salicylate intoxication all strongly suggest that salicylate intoxication was the cause of the fatal encephalopathy. Tetany developing in the course of salicylism has also been observed in 2 cases by Bergmark in his discussion of Odin's<sup>6</sup> paper.

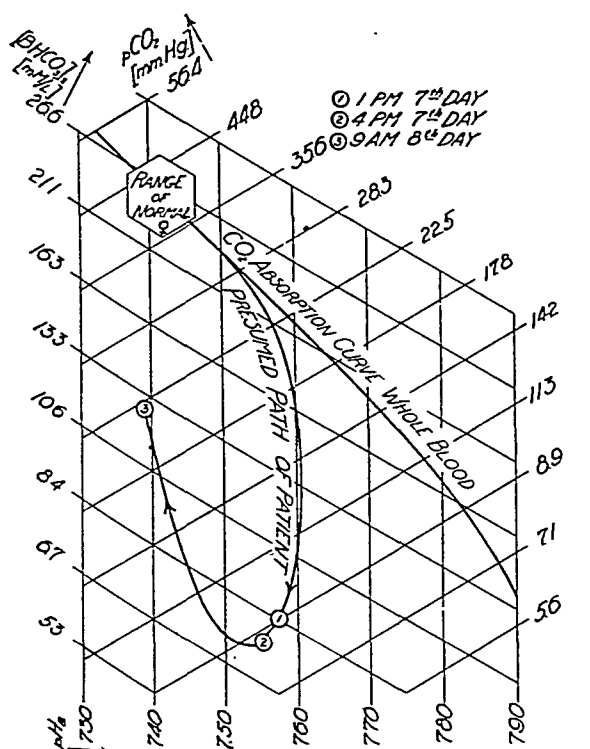


FIGURE 2. Acid-Base Balance Plotted on Trilinear Co-ordinates (after Shock and Hastings<sup>20</sup>).

The values for  $pCO_2$  (carbon dioxide tension) and  $[BHCO_3]$  (serum base bicarbonate) at points (1) and (3) were calculated from the pH and carbon dioxide content of the whole blood and hematocrit by the Shock and Hastings nomogram.<sup>21</sup> Point (2) was approximated from the assumption that the observed decrease in carbon dioxide content of the whole blood was associated with a slight fall in  $pCO_2$ . The normal values given are those of Shock and Hastings<sup>22</sup> and agree with our experience. The line marked "CO<sub>2</sub> absorption curve of whole blood" was approximated from the data of Van Slyke, Wu and McLean<sup>23</sup> on oxygenated horse blood with approximately the same HbO<sub>2</sub> (13.4 vol. per cent) as that of the patient (14.9 vol. per cent).

in the pH of the venous blood of patients suffering from salicylate intoxication and have since found a similar rise as the result of controlled salicylate administration. In the present case, the direction of the changes in the pH of the arterial blood and the carbon dioxide tension, together with the changes in urinary pH, indicate a primary respiratory alkalosis (Fig. 2).

in normal saline solution and containing 2.5 gm. of sodium sulfapyridine was administered intravenously. Twelve hours later, or 66 hours after the hyperventilation was first noted, the pulse became gradually more rapid and feeble and respirations ceased.

The time relations of significant data are shown in Figure 1.

**Autopsy.** Autopsy was performed 6 hours post mortem. There was gross and microscopic evidence of active rheumatic heart disease with pancarditis, and aortic and mitral valvulitis with mitral stenosis. There was chronic passive congestion of the liver and spleen and toxic changes in all the viscera. The left kidney was absent.

The gross changes encountered in the examination of the brain were confined to patchy subarachnoid effusions of blood, with small perivascular hemorrhages in the region of the 3rd ventricle and occasionally in the inferior portions of the basal

around blood vessels in the distended perivascular spaces. The large nerve cells were markedly diminished in the globus pallidus, and a scattered gliosis was observed throughout the basal ganglions, under the ependyma of the lateral and 3rd ventricles and in patchy areas in the deeper cortex.

No organisms were observed with the bacterial stains.

The anatomical diagnoses were as follows: active rheumatic myocarditis; aortic and mitral valvulitis; pericarditis; mitral stenosis; and nonspecific toxic encephalopathy.

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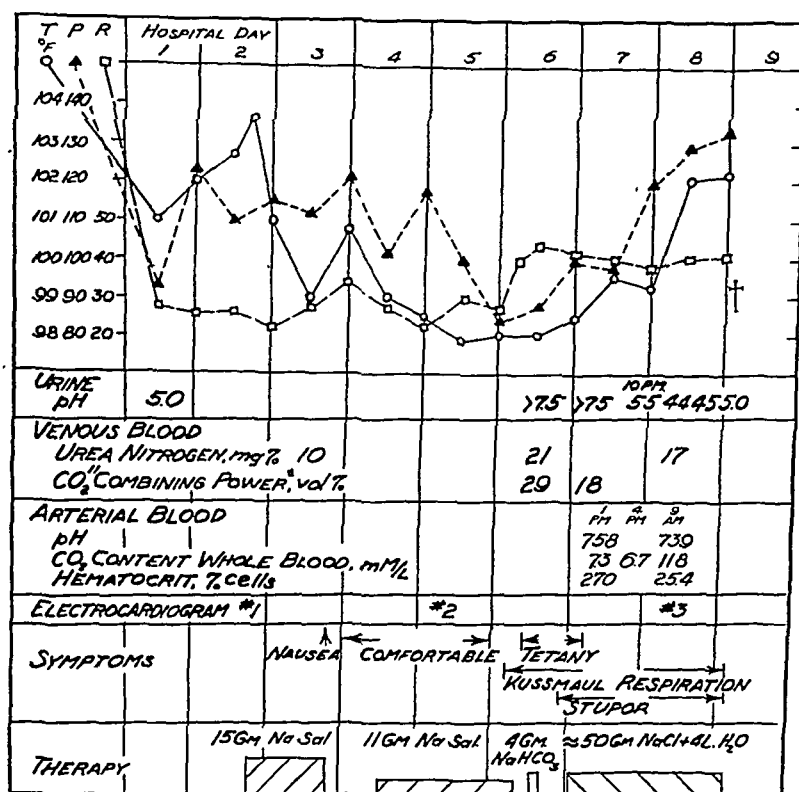


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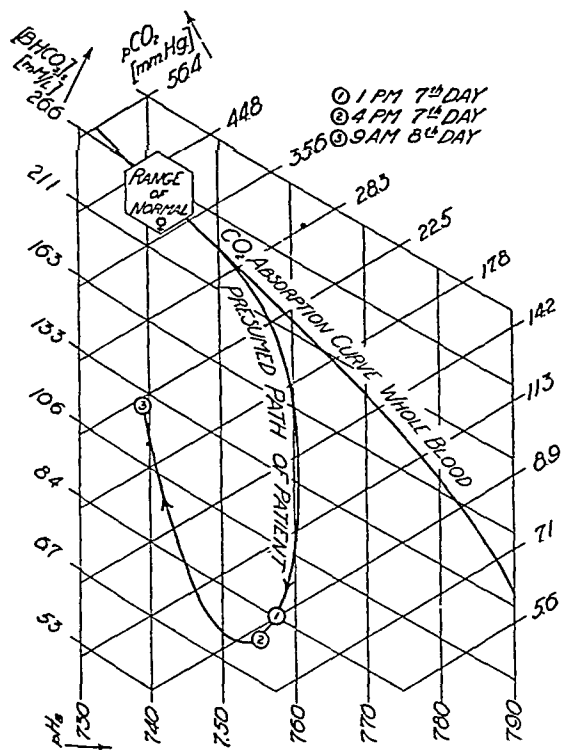


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Of further interest are the changes in the Q-T interval in the electrocardiogram (Fig. 3). The interval became prolonged to the upper limits of normal when tetany was present and the pH of the blood was high, but returned to its original average normal value during the period of compensation when tetany had disappeared and the pH had fallen to within normal limits.<sup>16</sup> Such changes in the Q-T interval in the absence of marked myocardial failure have usually been found in disorders associated with hypocalcemia and with respiratory and metabolic

effect of salicylate in any form is central respiratory stimulation. Partial correction of the acid-base balance caused no detectable improvement in the clinical condition.

Secondary manifestations of primary respiratory alkalosis — that is, tetany, prolongation of the Q-T interval and flattening of the T waves in the electrocardiogram, the secretion of alkaline urine during the development of the alkalosis and acid urine during its regression, and compensatory reduction of fixed base with lowering of the alkaline reserve — are recorded.

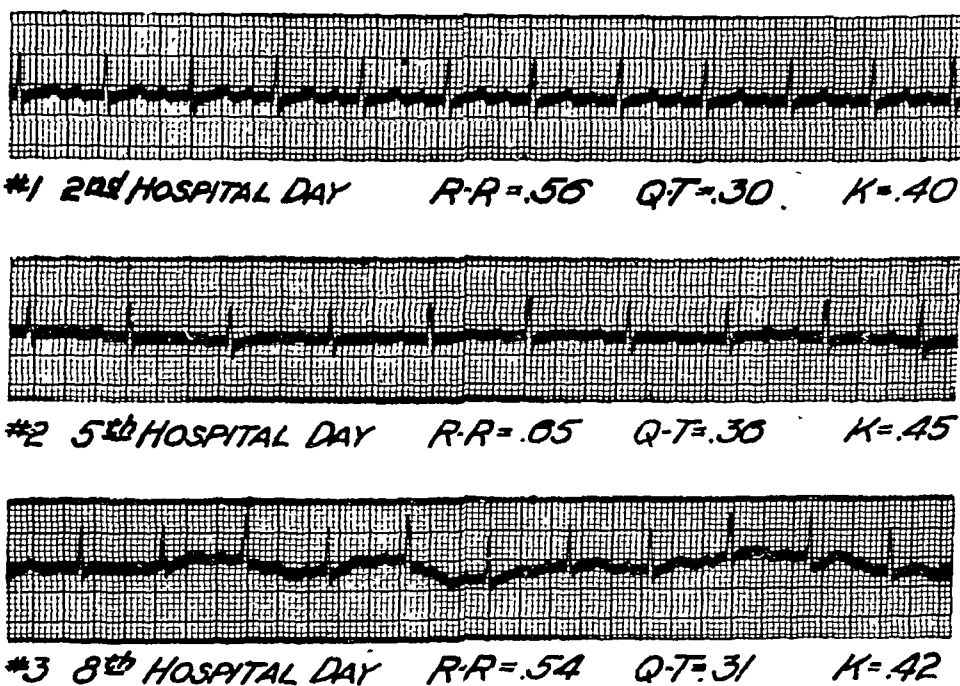


FIGURE 3. Serial Electrocardiogram Showing the Changes in the Q-T Interval during the Alkalosis (fifth hospital day).

Lead 1 is reproduced and not Lead 2, as suggested by Shipley and Hallaran,<sup>24</sup> because T<sub>2</sub> was isoelectric on the fifth hospital day; K is Bazett's cardiac index.<sup>25</sup>

alkalosis.<sup>17-19</sup> The serum calcium in this case was normal. Barker, Shrader and Ronzoni<sup>19</sup> noted flattening of the T waves in respiratory and metabolic alkalosis, a finding also present in this case.

The findings in this case, together with the literature cited, do not support the widely held belief that salicylate intoxication is an acidosis.

#### SUMMARY

A fatal case is recorded in which a primary respiratory alkalosis of extreme degree was conclusively demonstrated following salicylate administration.

The finding is in accord with acceptable data in the literature that indicate that the usual toxic

At autopsy a severe diffuse encephalopathy of the toxic type was found and described in detail.

The relative importance of the salicylate therapy and the acute rheumatic fever in the development of the encephalopathy is discussed.

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## MEDICAL PROGRESS

### ENDOSCOPY (Concluded)\*

EDWARD B. BENEDICT, M.D.†

BOSTON

#### ESOPHAGOSCOPY

##### Benign Tumor

Harrington and Moersch<sup>24</sup> regard benign tumors of the esophagus as potentially malignant, and point out that extensive operative procedures may be required for their removal. They are divided into two main groups: mucosal and extramucosal tumors. The mucosal tumors are often pedunculated and arise from the submucosa. They are usually fibrolipomas or fibromyxomas and are covered by normal epithelium of the esophagus. The extramucosal or intramural tumors arise from the muscle of the wall of the esophagus; they do not involve the mucosa and are usually leiomyomas. The growth of benign tumors of the esophagus is slow, and they may attain considerable size without giving rise to subjective symptoms. This is particularly true of the intramural tumors, which rarely produce obstruction of the esophagus unless they attain great size. The symptoms generally associated with these growths are dysphagia, substernal pain, regurgitation of food, cough and dyspnea. Pedunculated tumors are usually associated with obstructive symptoms, and the diagnosis of these growths is often definitely established by regurgitation of the tumor into the mouth, which may be the first subjective symptom. Regurgitation of these growths into the nasopharynx can imperil life owing to blocking of the trachea, which may result in strangulation. The roentgenographic and roent-

genoscopic examination of the esophagus is of great value in determining the presence of these growths. Esophagoscopy is of the utmost importance in establishing a definite diagnosis, although at times it may be difficult to determine the site of origin as well as the type of growth because of the difficulty in obtaining a specimen for biopsy through the normal esophageal mucosa. The site of origin of the pedunculated tumors can usually be definitely determined. The indications for surgical treatment of benign tumors are not so urgent or so imperative as those for malignant lesions of the esophagus. They depend somewhat on the patient's general condition, the amount of difficulty the tumor is causing and the site of the tumor. Inasmuch as such growths may undergo malignant change, these authors state that surgical treatment should be considered in all cases.

##### Carcinoma

Bersack<sup>35</sup> has reported a case of carcinoma of the esophagus in association with achalasia of the cardia. He is of the opinion that unless careful and repeated esophagoscopies are resorted to, carcinoma is rarely detected early in patients suffering from achalasia. No sharp change in the symptoms marks the appearance of carcinoma, especially when it is located high in the esophagus. This is so mainly because there is no interference with the passage of food. Even at the late stage at which cancer was detected in Bersack's case, no obstruction to the passage of the esophagoscope was encountered. Furthermore, small irregularities and

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filling defects in the dilated esophagus are often caused by, and are readily attributed to, retained secretion and food particles. In the case that Bersack reports the patient had suffered from a stricture of the cardiac end of the esophagus for ten years. The history revealed that she had been treated with dilatation, which had improved her condition for about five years. For the last four years, the patient regurgitated part of the food and found that food got stuck in the "pit of the stomach." The general condition was fair, and no anemia was present. The roentgenologic examination revealed a carcinoma in the middle of the esophagus and achalasia. The author stresses the fact that this was the first case among 227 cases of carcinoma of the esophagus that was preceded by achalasia. Since both conditions have a similar history, the author emphasizes the importance of an extremely careful examination.

In discussing carcinoma of the esophagus, Bird<sup>36</sup> stresses the importance of doing both esophagoscopy and bronchoscopy preoperatively, the object of the bronchoscopy being to demonstrate whether the lesion has extended into the trachea or left main bronchus in which case the lesion is definitely inoperable. Strieder<sup>37</sup> and Garlock<sup>26</sup> agree that preoperative bronchoscopy is of great importance in determining the operability of carcinoma of the esophagus.

### *Benign Stricture*

The management of benign stricture of the esophagus is a delicate problem. The dangers of blind bouginage cannot be too frequently emphasized. Eloesser<sup>38</sup> recalls the case of a benign lye stricture of the esophagus treated by blind bouginage by a local physician. The sound was apparently passed effectually, but still no food got into the stomach through the esophagus. The bouginage had been done some months previously without any obvious deleterious effects. When Eloesser opened the abdomen he found that the sound had been forced down retroperitoneally as far as the sacrum. On opening the chest, he of course found a fistula. Proceeding from there he was able to get a large bougie up into the mouth, and a large bougie was then introduced into the stomach from the upper esophageal segment.

Adams and Hoover<sup>39</sup> state that as a sequel to the treatment of carcinoma of the stomach by total gastrectomy and esophagojejunostomy in 68 patients, 6 of them developed a partial stricture at the anastomosis within a few weeks or months after the operation. All responded to repeated dilatations using a swallowed thread as a guide. The technic of successfully traversing a complete occlusion 2 cm. in length of the midthoracic esophagus by combined peroral esophagoscopy, retrograde esophagoscopy and mediastinotomy is described.

### *Cardiospasm*

According to Adams and Hoover<sup>39</sup> rapid dilatation with a modified Plummer bag in 2 cases of cardiospasm led to suppurative mediastinitis that required prompt surgical drainage. Both patients recovered. The authors were convinced that such rapid dilatation was too dangerous for further use. Henceforth, they intend to follow their former policy of gradual dilatation, accepting the inconveniences of slow dilatation and the time required rather than risking esophageal rupture. Leakage occurred in one case under general anesthesia, which was given at the insistence of an extremely nervous and temperamental patient. In addition, too great pressure was used. This complication must be classified as secondary to an error in judgment, since the pain reflex should be preserved as a safeguard during esophageal dilatation for cardiospasm.

Another complication of cardiospasm has been discussed by Gray and Jankelson<sup>40</sup> namely, inhalation pneumonitis resulting from overflow of food or secretions from the esophagus into the trachea. This pneumonitis may be either of the recurrent acute type or of the chronic type with acute exacerbations. The alleviation of the cardiospasm by bouginage improves the general condition and contributes to the cure of the pneumonic process. It is recommended that the esophagus be investigated routinely in all cases of etiologically obscure chronic pneumonitis or recurrent acute pneumonia.

Garlock<sup>26</sup> emphasizes the importance of esophagoscopy in cardiospasm. The finding of a smooth conical obstruction at the lower end of the esophagus in the x-ray picture does not necessarily indicate a benign cardiospasm. Esophagoscopy must be carried out. Negative esophagoscopy findings do not exclude completely the presence of a cardiac carcinoma. Repeated endoscopic examinations are indicated if the symptoms persist. No patient should be subjected to operation unless the biopsy specimen obtained by esophagoscopy shows carcinoma. It must be emphasized that the care of a patient with cancer of the esophagus is a co-operative problem requiring the concerted efforts of the roentgenologist, esophagoscopist, anesthetist, operating room staff, bedside nurses, physician and surgeon. Even under the most ideal conditions, the operative mortality is relatively high if the surgeon does not practice careful selection of his operative material.

In discussing the respiratory complication of achalasia of the cardia (cardiospasm) with megaesophagus, Hurst<sup>41</sup> states that it is not generally recognized that symptoms may arise from pressure by the distended esophagus or from aspiration of regurgitated food. In 1 case reported, sudden death occurred from asphyxia.

### *Hysterical Dysphagia*

Gaarde and Olsen<sup>42</sup> have classified the causes of dysphagia in the upper part of the esophagus. In discussing functional conditions, they distinguish between hysterical dysphagia and functional dysphagia. They regard hysterical dysphagia as a well-defined clinical syndrome that affects elderly women with anemia and is usually accompanied by loss of weight and nutritional deficiency. It is ordinarily referred to as the Plummer-Vinson syndrome. The cricopharyngeus muscle fails to relax and allow passage of food. An esophageal web frequently occurs just below the level of the cricopharyngeus muscle. This web consists of fibrous strands that traverse the esophageal lumen. Whether iron-deficiency anemia or psychic trauma is the antecedent factor in these cases is difficult to determine. The dramatic relief of dysphagia produced by the passage of an esophagoscope or dilating sound suggests that a cure is effected by release of cricopharyngeal spasm, dilatation of any organic stenosis present and the restoration of the patient's confidence in his ability to swallow. The subsequent administration of iron and vitamins should result in permanent relief of symptoms. Attention is called to the frequency with which carcinoma develops at the esophageal introitus in cases of the Plummer-Vinson syndrome.

### *Functional Dysphagia*

Functional dysphagia, on the other hand, according to Gaarde and Olsen<sup>42</sup> is less clear cut than is the Plummer-Vinson syndrome. Emotionally unstable patients of either sex are likely to complain of difficulty in swallowing. Fear of choking is often the most prominent symptom, and these patients may have equal difficulty in swallowing liquid and solid foods. The diagnosis of functional dysphagia may be dangerous. When dysphagia referable to the hypopharynx or upper part of the esophagus affects a psychoneurotic patient, it is a general practice to make a diagnosis of functional dysphagia. Unless esophagoscopic examination is carried out, errors in diagnosis may readily occur. Organic lesions of the upper part of the esophagus may be confused with functional dysphagia.

### *Myasthenia Gravis*

Blalock,<sup>43</sup> in a discussion of thymectomy in the treatment of myasthenia gravis, states that 14 of 20 patients studied complained of difficulty in swallowing. This disease must therefore be considered in patients with dysphagia. Other more frequent causes of dysphagia must be excluded by x-ray and esophagoscopy. The neostigmines (Prostigmin) test is helpful in the diagnosis. The pre-operative neostigmine requirements of these patients varied from 75 to 910 mg. daily. Death in 1 case following thymectomy was due to atelectasis and respiratory failure. In this case Blalock be-

lieves that bronchoscopy and aspiration were definitely indicated. In summarizing the results of thymectomy, performed on 20 patients with severe myasthenia gravis during the last three years, Blalock states that a benign thymic tumor was found in only 2. Four of the patients have died since operation, 3 of the deaths occurring in the early postoperative period. Of the 16 remaining patients, 3 are essentially well, 5 are considered improved, 5 are moderately improved, and 3 have shown little if any improvement. All the 16 surviving patients expressed the opinion that the operation had been helpful.

### *Peptic Ulcer of the Esophagus*

It has been noted by Adams and Hoover<sup>39</sup> that a large percentage of patients with peptic ulcer of the lower end of the esophagus have a short esophagus and a small diaphragmatic hernia.

Lust and Peskin<sup>44</sup> have studied the roentgenologic diagnosis of peptic ulcer of the esophagus, stating that without doubt diagnoses are most accurate when made by direct visualization of the process. Esophagoscopy, however, is a procedure that causes great discomfort, and it should be performed only by those skilled in its technic. Lust and Peskin believe that careful roentgenologic examination can demonstrate the lesion with sufficient accuracy. I take exception to this statement, believing that in any case of narrowing or ulceration of the esophagus, esophagoscopy and biopsy must be performed to exclude carcinoma; esophagoscopy and bouginage may also be necessary for therapeutic purposes. In skilled hands, with a reasonably co-operative patient, the procedure is not one of great discomfort.

### *Experimental Peptic Ulcer of Esophagus*

Brown<sup>45</sup> fed white rats a long-continued, vitamin-deficient, rice diet and noted frequent lesions of the esophagus consisting of focal ulcerations of the mucosa, with penetrating inflammation, mucosal hyperkeratosis, edema of the submucosa, atrophy and fibrosis of the muscularis and dilatation of the organ. After the administration of synthetic vitamins, the rats gained in weight, the ulcers largely healed and the autopsied animals showed practically no lesions in the internal viscera. The authors concluded that the lesions noted in these animals appeared to be of dietary origin.

### *Spontaneous Rupture of Esophagus*

Collis, Humphreys and Bond<sup>46</sup> report the spontaneous rupture of the esophagus after a heavy meal occurring in a man forty-one years of age with a previous history of dyspepsia. This condition should be kept in mind when doubt is felt about the diagnosis of perforated peptic ulcer. Deep emphysema in the neck is an important physical sign. Suturing

of the tear in the esophagus, combined with drainage of the pleural cavity on the affected side, offers the best chance of recovery.

## GASTROSCOPY

### *Instruments*

Hardt<sup>47</sup> has described a new flexi-rigid gastro-scope consisting of two parts, a flexible sheath and a removable interior consisting of a rigid optical system comprised of approximately twenty-five optical elements. The optical system is inserted into the sheath when the latter is in place in the stomach. Hardt claims that the advantages of this gastroscope are an increased angle of visualization, a larger image, diminution in the blind-spot areas, a better view of the antrum and less gagging by the patient.

Equen<sup>48</sup> describes a new magnet for removing foreign bodies in the food and air passages. The magnet is made of cast Alnico and is attached to a Levine tube, through which a metal stilet has been inserted to increase the motility of the tube. The other end of the Levine tube is attached to a rubber bulb, this apparatus being used for inflating the stomach. In the case reported, a bobby pin was successfully removed from the stomach of a nineteen-month-old baby under fluoroscopic visualization. The entire procedure lasted only eight minutes.

The whole foreign-body problem would be greatly simplified if patients vomit foreign bodies as easily as occurred in the case reported by Benedict.<sup>49</sup> In this very exceptional case, a three-year-old child swallowed an open safety pin a few minutes before entering the Emergency Ward. A few hours later, the patient vomited and the pin was recovered. It measured 2.7 cm. in length. The reason it was vomited so readily was that the point was bent toward the keeper.

### *Gastritis*

Renshaw<sup>50</sup> believes that the principal value of gastroscopy lies in the diagnosis of gastritis. With rare exceptions gastroscopy is the only clinical means for establishing this diagnosis. Although the true significance of the mucosal changes noted gastroscopically has not been definitely settled, chronic gastritis undoubtedly is a definite entity, which at times produces severe symptoms. A small percentage of cases of unexplained massive hemorrhage from the upper gastrointestinal tract have been shown to be due to chronic gastritis. Renshaw quotes Bockus as stating that unquestionably the flexible gastroscope is opening up new diagnostic channels.

Benedict<sup>51</sup> has written a review of gastroscopy. He concludes that gastroscopy with the flexible gastroscope is an easy and safe procedure, the value of which cannot be doubted. Attention is called to the omni-angle feature and the controllable

flexibility of certain instruments. The simpler technics, including 4 per cent cocaine gargle and small pillows for head support, are preferred to more complicated methods. The indications for gastroscopy are outlined. He states that no stomach that is producing symptoms should be considered normal without gastroscopic study and that the significance of hemorrhage in gastritis has been demonstrated by gastroscopy. Gastroscopic and pathologic findings in gastritis are correlated. The usefulness of gastroscopy in cases of gastritis, ulcer and tumor is critically considered.

Meyer and Steigmann<sup>52</sup> have discussed the surgical treatment of corrosive gastritis. They state that dysphagia appears oftener and sooner after the ingestion of an alkaline corrosive (lye) than after that of an acid. In fact, in most cases of corrosive gastritis due to an acid, the patients presented themselves not because of dysphagia but because of symptoms of gastric obstruction. Corrosive gastritis may be confused with gastric carcinoma, not only because of the suggestive appearance of the x-ray films but also because of symptoms of continuing vomiting, marked weight loss and achlorhydria. The importance of differentiating the two conditions is obvious from the point of view of treatment, as well as from the point of view of prognosis. Gastroenterostomy may be done rather than resection inasmuch as the dangers of gastrojejunostomy are minimal, since in these stomachs there is no free acidity.

In a study of peptic ulcer, gastritis and psychoneurosis among naval personnel suffering from dyspepsia, Montgomery, Schindler, Underdahl, Butt and Walters<sup>53</sup> studied 45 unselected patients, finding 23 cases of duodenal ulcer and 22 cases showing no ulcer. In 11 of the latter the gastric mucosa proved to be entirely normal gastroscopically, but in the remaining 11 cases there were varying degrees of hypertrophic, superficial and atrophic gastritis. In 11 cases, there was a definite psychoneurosis of the anxiety and mixed types sufficiently severe to necessitate discharge from the service. In summarizing the differential diagnoses in this group, it is interesting that among these 22 cases there were 11 in which the diagnosis was made by psychiatric approach. In the other 2 neither psychiatric, gastroscopic nor any other study afforded a satisfactory diagnosis.

In a comparison of the radiologic and gastroscopic findings in 200 dyspeptic soldiers, Guyer<sup>54</sup> states that the reason for the discrepancies between them is not difficult to determine. The radiologist examines the stomach as a whole, his diagnosis resting on the estimation of function, with an examination of the coarser anatomic details. The gastroscopist, on the other hand, is in a position to examine closely the changes in the mucous membrane, seeing the early inflammatory changes that may be taking place, as well as ascertaining the

more obvious organic lesions, such as ulceration and malignant change. In the study of the duodenum, radiology so far stands supreme, and any changes seen in the stomach by the gastroscopist are merely corroborative and not diagnostic, since the duodenum is at present inaccessible to him. In cases in which radiology has failed to elicit any cause in a complaint of a dyspeptic nature, gastroscopy is of great assistance, mainly in the diagnosis of gastritis, since in this disease the gastroscopic findings are considerably more helpful than is radiology. Two other types of case offer considerable scope for the combination of the two methods of examination, — cases of healed or healing gastric ulcer, which has passed beyond the stage where it was possible to demonstrate it radiologically, and cases in which there is a question of early malignant disease but in which the organic changes are sufficiently marked to allow radiologic demonstration. Gastroscopy in the armed services has obvious limitations. It is considered of use in patients constantly reporting sick with dyspeptic symptoms when all other forms of investigation have been negative. The demonstration of gastritis in a case of this type is important to facilitate the patient's treatment or disposal. Two hundred cases of dyspepsia in serving soldiers were examined radiologically and gastroscopically. Both types of diagnoses are discussed separately, and the combined findings of the two methods are analyzed. The conclusions reached are that the two investigations are complementary to each other, but that in the study of gastritis, gastroscopy gives more valuable information than can be obtained by radiology.

Scheff, Horner and Kenamore<sup>55</sup> believe the incidence of gastritis in patients with duodenal ulcer, as determined by gastroscopic examination, is higher when the ulcer is complicated by pyloric obstruction. Eighty-six per cent of patients with duodenal ulcer and obstruction showed the mucosal changes of superficial gastritis, whereas 62 per cent of the nonobstructed group gave similar findings. Severe gastritis was found six times more frequently in the stasis group. It appears that retention of gastric contents is associated with inflammatory changes in the gastric mucosa.

Warren and Meissner<sup>56</sup> are of the opinion that in the severe stages of chronic gastritis the epithelium assumes alterations that are entirely comparable to well-recognized premalignant lesions in the cervix, breast and skin. The most important of these changes are the presence of atypical cells and atypical glands and increased mitotic activity. Only the severe stage of chronic gastritis with these marked epithelial alterations shows the necessary criteria for premalignancy; the mere presence of mucosal infiltration by inflammatory cells and of slight alterations of the epithelium is not sufficient. These authors conclude as follows: chronic gastritis is a

labile condition that may regress and that need not necessarily progress; not all stages or types of chronic gastritis can be considered to be precancerous: the histologic changes in chronic gastritis should be divided into exudative and epithelial, the former having no direct significance as a precancerous lesion; when epithelial changes become severe, they may be comparable to well-recognized premalignant lesions elsewhere in the body; and since one stage of chronic gastritis meets the necessary criteria for a precancerous lesion, it may be assumed that some gastric cancers arise on this basis.

### *Gastric Ulcer*

In discussing the treatment of gastric ulcer, Counseller, Waugh and Clagett<sup>57</sup> note that they are operating more frequently on gastric ulcer than formerly. The lesions that are not immediately treated surgically are treated medically in the hospital. If the ulcer becomes smaller or disappears, as determined roentgenologically and by gastroscopic examinations, and if occult blood disappears from the stools, medical management is continued. Periodic examinations are strongly advised. When this type of response is not obtained by medical treatment, patients are advised to have surgical treatment at once.

### *Carcinoma*

As regards carcinoma, Counseller, Waugh and Clagett<sup>57</sup> believe that the general trend of medicine is toward a more and more complete examination, and since early carcinoma can be visualized either at the time of roentgen-ray examination or through the gastroscope or both, it is probable that the more frequent use of these procedures in the future will increase the operability rate of carcinoma of the stomach.

Palmer and Humphreys<sup>58</sup> discuss 4 cases of peptic ulcer and healing in gastric carcinoma. In all of them, the duration and history were compatible with primary ulcerating neoplasm and gastroscopic evidence of neoplastic infiltration was found at the first examination. In discussing these cases Fitzgibbon reported the case of a penetrating ulcer crater that filled in gastroscopically after eight months of treatment so that the bottom could not be seen. At the end of three and a half months, the lesion was completely covered by mucosa. Surgery had been advised but refused. A few months later, symptoms recurred. Gastroscopy and x-ray examination both showed carcinoma, but the lesion was inoperable, since liver metastases were present.

### *Lymphosarcoma*

Paul and Parkin<sup>59</sup> made gastroscopic observations on a patient with lymphosarcoma of the stomach. From the standpoint of visualization of the lesion with the gastroscope, they do not believe

of the tear in the esophagus, combined with drainage of the pleural cavity on the affected side, offers the best chance of recovery.

## GASTROSCOPY

### *Instruments*

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According to Ruiz, Zamanillo and Salar,<sup>64</sup> the frequency of primary cancer of the liver without cirrhosis as reported in the literature is 1:1000. Primary cancer of the liver without cirrhosis can be differentiated from either primary cancer of a cirrhotic liver or secondary hepatic cancer by the rapid enlargement of the liver, its firmness, a smooth, hard border on palpation, moderate ascites and the acute course of the disease, which varies between four and five months after the onset of the symptoms. I believe that such a differential diagnosis is not possible on the basis of symptoms or physical signs. Even with peritoneoscopic biopsy, such a diagnosis may be difficult.

Kennaway<sup>65</sup> has examined the incidence of primary carcinoma of the liver in the Negro in Africa, comparing it with the incidence of the same lesion in the Negro in the United States. He concludes that such data as are available suggest that the high incidence of primary cancer of the liver found among Negroes in Africa does not appear among Negroes in the United States and is therefore not of purely racial character. The prevalence of this form of cancer in Africa may be due to some as yet unidentified extrinsic factor. The statistical evidence concerning this question is confused by the inclusion of cancer of the gall bladder in the same category with cancer of the liver

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that there were sufficient features to permit identification of the lesion as a lymphosarcoma. The consensus in current radiologic literature is that there are no positive diagnostic points on roentgen-ray examination.

### *Gastric Diverticulum*

Whitehouse and MacMillan<sup>60</sup> believe that gastroscopy is helpful in the diagnosis of diverticula of the stomach. They believe that one can evaluate the size of the opening more accurately by means of the gastroscope, since the stomach is inflated and the diverticulum ballooned out. In 2 cases reported, they were able to see the interior of the sac almost completely and considered this of value in ruling out an ulcer or tumor in the diverticulum.

### PERITONEOSCOPY

According to Benedict,<sup>61</sup> one of the chief uses of the peritoneoscope is in the diagnosis of liver disease. When one considers that many of these patients are seriously ill and that in most of them an exploratory laparotomy is out of the question, the value of a precise diagnosis by peritoneoscopy is apparent. The cases referred for peritoneoscopy because of liver diseases usually fall into one of the following groups.

*Metastatic carcinoma.* In this group there is a positive or presumptive clinical diagnosis of carcinoma of the breast, bronchus, esophagus, stomach, pancreas, colon, rectum, prostate or the like, and before planning medical, x-ray or surgical treatment, it may be of great importance to know whether or not there is metastatic disease in the liver.

*Hepatomegaly.* Is one dealing with metastatic or primary carcinoma, cirrhosis, hepatitis, sarcoma, echinococcal cyst, polycystic liver or some other liver disease?

*Ascites.* Is this due to cirrhosis, carcinoma or tuberculous peritonitis?

*Jaundice.* Is the diagnosis toxic cirrhosis, biliary cirrhosis, malignant neoplasm, hepatitis or some other infectious process?

*Doubtful clinical findings.* What is the precise diagnosis?

In conclusion it is stated that peritoneoscopy is an important and well-established method of examining the peritoneal cavity that is especially applicable to the differential diagnosis of liver disease. With biopsy, a suspected diagnosis is made positive. In a series of peritoneoscopies in 435 patients, the examination was undertaken primarily to study the liver in over two thirds of the cases. One hundred and seventy patients were found to have metastatic carcinoma, 73 had cirrhosis, and the remainder had various diseases, including hepatoma, sarcoma, lymphoma, lymphangioma, Banti's disease, cholangitis, polycystic liver, echinococcal cyst and sarcoid.

Wershub<sup>62</sup> also finds the peritoneoscope of great value in the diagnosis of liver disease, concluding as follows. The peritoneoscope has specific indications for its use, and is especially applicable to the diagnosis of liver disease. The indications previously expressed are definite and in some cases offer the only means, other than exploratory laparotomy, for diagnosis. The diagnosis of portal cirrhosis, which so frequently cannot be accurately determined clinically, can be made with 100 per cent accuracy by the peritoneoscope. In other hepatic disorders, the endoscopic impression may confirm or establish a diagnosis.

Mensch and Hanno<sup>63</sup> have discussed a case of hepatoma of the liver with metastasis to bone occurring in a patient known to have had advanced cirrhosis eight years previously. A number of features in this case are worthy of comment. The absence of abnormalities in a number of tests of liver function and of any of the clinical features generally encountered in cirrhosis at a time when the liver of this patient was frankly cirrhotic is of interest. The patient showed a pathologic urobilinogenuria, a slight hypoproteinemia and some retention of dye with the 5-mg. dose of bromsulfalein. On the other hand, the Takata-Ara and the galactose tolerance tests were negative and there was no dye retention with the 2-mg. dose of bromsulfalein. These findings serve to emphasize the now well-known fact that any given test of liver function may be negative despite the presence of a frankly cirrhotic liver. There are to these authors' knowledge no references in the literature to the length of survival of patients following the demonstration of a frank cirrhosis of the liver in the absence of clinical or laboratory evidences of hepatic decompensation. All the figures usually given for the duration of life in patients with portal cirrhosis are calculated from the time of onset of symptoms or findings to which the hepatic disease has given rise. It is important, however, for it is to be realized that the existence of a cirrhotic liver may well antedate by a considerable number of years the manifestations of clinical portal cirrhosis. The relation between malignant primary tumors, especially hepatoma, and cirrhosis of the liver is striking. According to the consensus of a number of observers, upward of 75 per cent of cases of hepatoma are associated with cirrhosis. Whether an antecedent cirrhosis plays a role in the subsequent development of the carcinoma, as is the belief of most observers, whether cirrhosis follows carcinoma, as Wegelin propounded, or whether the two conditions occur independently cannot, of course, be determined by a single case. This report, however, does emphasize the association of the two conditions, and in this one case, at least, conclusively shows that the cirrhosis preceded the hepatoma by at least several years. The presence of metastasis to bone in cases of hepatoma of the liver is generally considered extremely rare.

The caloric and electrolyte needs could scarcely be met in view of the ileostomy loss, which was enhanced by the obstruction proximal to the stoma. His weight fell 21 pounds in four weeks; he became weaker and his skin lesions became worse. This situation, in addition to the development of bleeding from the ileostomy, presumably due to the repeated catheterization, brought about a decision to operate again to relieve the mechanical obstruction, if possible.

At the second operation, one month after the first, the small bowel was found uniformly dilated with no single obstructive point. There was a twist several centimeters proximal to the stoma but no clear-cut obstruction. The serosa, however, was cyanotic, with dilated, almost "varicose" veins in the mesentery. No obstruction to venous return could be found to explain this. On the serosa were several thin white plaques, where the wall of the bowel seemed extremely thin. No change in the ileostomy was made. His general course was little altered by operation.

Two days later the patient was suddenly seized with a severe midabdominal pain that became generalized; the abdomen was board-like, and he went into shock and died in the course of two hours.

#### DIFFERENTIAL DIAGNOSIS

DR. HELEN S. PITTMAN: This is a long case, and I do not believe that there should be much discussion about the diagnosis. There may be a few atypical features and a few complicating factors, but by and large this is a classic case of chronic idiopathic ulcerative colitis occurring in a young man with a characteristic unhappy social background, which is important. He had a family situation that was thoroughly bad. The patient was an unhappy spontaneous person who did not make close friendships and was the sort of person in whom ulcerative colitis may develop.

Then we go back in the past history and see that at thirteen, five years before entry, he began to have trouble with the gastrointestinal tract. One year after that, at the age of fourteen, he had an appendectomy. Almost surely he did not have acute appendicitis but, rather, ulcerative colitis. I think that it is usually the patient with regional enteritis, rather than colitis, who comes to the hospital after having had a previous appendectomy, and the patient with ulcerative colitis may come after hemorrhoidectomy, both of which are mistaken diagnoses. But I am quite sure that this operation four years before entry was performed because of symptoms due to ulcerative colitis and that it threw him right over into the frank clinical colitis, because on the day following operation he had twenty-five stools. He went along, probably without anyone really understanding what was going on, for quite a long time. It was not until two and a half years later that he went to a hospital for

treatment, and it was at that time that the diagnosis "colitis with infection" was made. He apparently did well on a low-residue diet. He continued to grow, but it seems to me that a great many of these young people with ulcerative colitis have fairly big frames, so there is nothing too surprising about that. He had lost 11 pounds preceding entry, which in an eighteen-year-old boy is quite a lot.

He had pneumonia at the age of seven years, which I put down as a positive finding but not relevant, any more than the "fits," which may have been due to epilepsy or something entirely different.

On examination he was pale, had skin lesions, a dirty mouth and clubbing of the fingers and toes; the last is not an infrequent finding in long-standing ulcerative colitis. He had cold moist hands, a finding perfectly compatible with that disease. He came in with a rather rapid pulse, minimal fever, mild anemia and slight leukocytosis. They happened to catch one stool without blood, but the rest were consistently guaiac positive. Amebas were looked for, but amebic infestation can probably be discarded. On admission the blood chemical values were normal, with a high normal chloride level, which probably means that he had not been having violent diarrhea before he came in. The prothrombin time was prolonged, which is frequent in these patients, all of whom have inadequate nutrition, including a deficiency of vitamin K. A barium enema showed changes characteristic of long-standing extensive idiopathic ulcerative colitis. Do the films show anything additional?

DR. MILFORD D. SCHULZ: This is certainly the typical appearance of ulcerative colitis — shortened rigid walls, which do not collapse well on evacuation, and a granular mucosa. There are only a few ulcers.

DR. PITTMAN: Ulcers lower down were seen through the sigmoidoscope. How big is the spleen?

DR. SCHULZ: The tip of the spleen reaches below the costal margin, but it is not extraordinarily large.

DR. PITTMAN: This boy of eighteen, having been ill for four years, probably five, came in with the advanced irreparable changes of chronic ulcerative colitis; he was carried along medically in an attempt to see what could be done by replacement therapy. He had profuse diarrhea, treated symptomatically, and then was started on sulfasuccidine, which is the drug of choice in afebrile ulcerative colitis, — this boy was essentially afebrile, — and a fairly good caloric intake. Proctoscopic examination showed characteristic lesions — a scarred, fibrotic, granular, hyperemic colon, with many ulcers of various sizes, most of them oozing profusely. A second barium enema suggested that the process was advancing. An ileostomy was then performed. He apparently was in reasonably good shape at that time, and I gather that it was not done in the sense of emergency. Sometimes as such it is a life-saving measure. It was presumably done because it was thought that nothing could be accomplished medi-

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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#### CASE 31211

##### PRESENTATION OF CASE

An eighteen-year-old boy was admitted to the hospital because of severe diarrhea and weight loss.

Five years before admission, at the age of thirteen, the patient began to have episodes of moderately severe epigastric and precordial pain not related to meals; these occurred about twice a week and were usually relieved by belching. There was increased perspiration, and occasional vomiting without nausea. At the age of fourteen he had an appendectomy following a period of unknown duration of severe pain in the right lower quadrant of the abdomen, without vomiting. On the day following the operation he had about twenty-five stools. In the course of a month the number of stools decreased gradually, yet averaged ten to twelve per day, usually with mucus and occasionally with blood. From that time on the diarrhea never disappeared. One and a half years before entry he was admitted to another hospital, where a diagnosis of "colitis with infection" was made. He was treated with a low-residue diet and was discharged moderately improved. He had progressively less pain, tenesmus and urgency during the year before admission. He continued to grow but had lost 11 pounds during recent months.

The boy's parents were divorced when he was three years old. The patient lived with his mother and grandmother. The mother was a shoe-factory worker and was described by the patient as nervous and pessimistic. The patient did not make close friendships. Until he was seven years old he had had "fits" or convulsions about twice a year. He had had pneumonia at seven years of age.

Physical examination revealed an asthenic, poorly nourished but fairly well developed young man. The skin was pale, with "pimplés" over the back. The teeth were carious, and oral hygiene was poor. There was clubbing of the fingers and toes, and slight tremor of the hands, which were always cold and moist. The lungs were clear, and the heart was normal. The abdomen showed one small area of slight deep tenderness with minimal spasm in the left lower quadrant. Neurologic examination was negative.

\*On leave of absence.

The temperature was 99.5°F., the pulse 90, and the respirations 20. The blood pressure was 105 systolic, 65 diastolic.

Examination of the blood showed a red-cell count of 4,200,000; in the smear there was hypochromia with some poikilocytosis and anisocytosis. The platelets were greatly increased. The white-cell count was 12,750, with 2 to 8 per cent monocytes and some toxic granules in the neutrophils. The urine was normal. The first stool examined was guaiac negative, but later the stools showed +++ guaiac tests. Repeated cultures were negative for pathogens, and no amebas were found. The serum nonprotein nitrogen was 23 mg. per 100 cc., and the chloride 105 milliequiv. per liter. The prothrombin time was 30 seconds (normal, 18 to 20 seconds). A Hinton test was negative.

A barium enema showed the barium to pass rapidly through a tube-like sigmoid and colon into the proximal portion of the terminal ileum. The bowel was extremely irritable, spastic and stiff. The spleen appeared enlarged.

The patient had three to sixteen bowel movements a day for the first six weeks. He received many transfusions of whole blood and plasma. The daily caloric intake was irregular but remained largely between 2000 and 3000 calories. He received sedatives, bismuth subcarbonate and belladonna during the first two weeks, then was given 14 gm. of sulfasuccidine a day. Proctoscopy to the level of the sigmoid revealed an extremely irritable, scarred colon with fibrosis and granularity; in some areas there was marked hyperemia, with large and small ulcerations, most of which oozed blood profusely. A barium enema four weeks after admission suggested advancement of the disease. The ileum did not fill.

Six weeks after admission an ileostomy was performed under local and Pentothal anesthesia. The surgeon noted that the cecum was pale and thickened. The terminal ileum appeared normal. It was divided 10 cm. from the ileocecal valve, and the proximal end brought through the abdominal wall. He drained from 1200 to 4700 cc. daily from the ileostomy and developed severe vomiting.

On the third postoperative day he developed right carpedal spasm. He had a negative Trouseau sign. The serum calcium was 9.8 mg. per 100 cc., and the phosphorus 4.4 mg.; the sodium was 128 milliequiv. per liter, and the chloride 84 milliequiv. Despite vigorous sodium chloride therapy, the serum chloride rose very slowly. A week after operation the small bowel became distended and abdominal cramps became quite severe. A Miller-Abbott tube brought some relief. It was soon found that there was an intermittent obstruction a few centimeters within the ileostomy and that about six catheterizations of the ileum daily afforded relief of the cramps.

## DR. PITTMAN'S DIAGNOSES

Chronic idiopathic ulcerative colitis.  
Dietary deficiency, chronic.  
Perforation of ileum.

## ANATOMICAL DIAGNOSES

Chronic ulcerative colitis.  
Acute ulcerative ileitis, with perforation.

that were seen at operation. The entire colon was extremely thick, and the lumen was narrowed — a true "garden hose" variety (Fig. 1). The process in the colon was practically healed, and we were unable to find any extensive acute ulcers. The ileum, on the other hand, was markedly hemorrhagic and very thin, and when opened, there were numerous ulcers measuring 1 to 2 cm. in diameter,

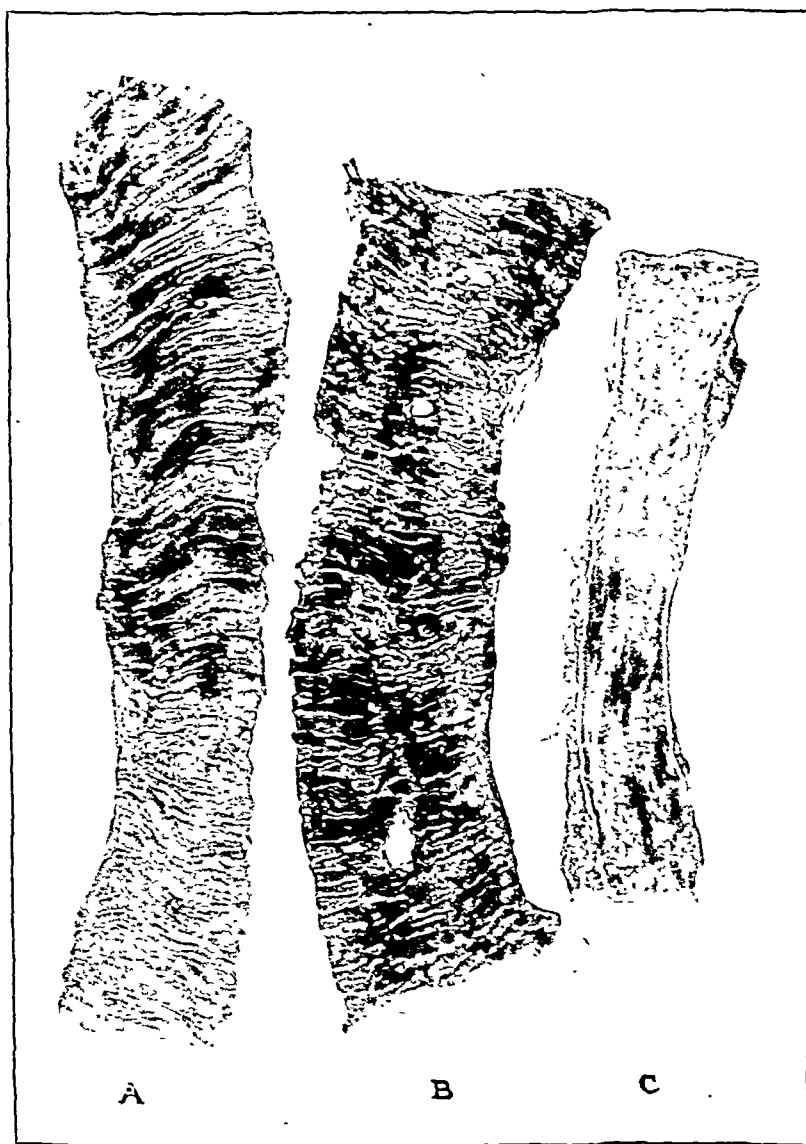


FIGURE 1. Photographs of Sections of the Small and Large Bowel.  
A — acute ulcerations of ileum; B — perforated ulcerations of ileum; C — chronic fibrotic lesions of colon.

Acute generalized peritonitis.  
Operations: ileostomy; laparotomy

## PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy showed an extensive infection of the peritoneal cavity and perforation of several of the thin areas in the terminal ileum

three of which had perforated. These ulcerations occurred only in the proximal loop of the ileostomy. The distal loop of ileum was perfectly normal, showing no evidence of edema, hemorrhage or anything that suggested ileitis. This suggests that the disease that we found in the terminal ileum was not present at the time of the ileostomy but had occurred follow-

cally and that the only thing to do was to put the bowel at rest. At operation the surgeon noted that the cecum was pale and thickened. In other words the patient had changes as far up as the cecum. Whether there was a secondary factor, such as tuberculosis, I do not know. I am inclined to think that there was none and that the process was merely extensive, involving the whole colon.

Following ileostomy the patient got into trouble right away. Carpopedal spasm was present on the third day, with low phosphorus and chloride levels and so forth. I assume that these findings were probably due to the tetany that one finds with vomiting and loss of chloride, although certainly it is not uncommon to see tetany, with a change in the phosphorus and calcium levels, in long-standing intestinal disease of this sort.

Then began the postoperative battle to keep up the intake, and in this case the battle was lost. They began catheterization of the ileostomy, which is a questionable procedure. I believe that Dr. Moore and Dr. McKittrick think that, in general, dilatation of the stoma is safer than catheterization. The patient began to bleed, and it may well have been from the trauma of the catheterization, but we have no data concerning the prothrombin level at that time. The chances are that it was greatly prolonged. He had been losing large amounts of fluid and had not been able to maintain the chloride level. A second operation became imperative, and they found a uniform dilatation of the small bowel without definite obstruction. The serosa was cyanotic, and dilated veins were seen in the mesentery. I do not know what that was, unless edema of the tissues interfered with venous return. The serosal plaques again make one wonder whether to bring in tuberculosis, but I do not believe that it is necessary. They were thin plaques; with little left of the bowel wall, and probably one of these plaques was responsible for the terminal event two days later.

My diagnosis is chronic idiopathic ulcerative colitis, with a chronic deficiency state on entry because of several years of diarrhea. The dramatic episode was acute perforation of the small bowel, likely through one of the thin areas noted at the second operation.

DR. BENJAMIN CASTLEMAN: What do you think the pale areas in the small bowel wall were?

DR. PITTMAN: I think that they were areas of ulceration where the serosa was extremely thin, because they were described as being transparent. I do not believe that they were tubercles.

DR. WYMAN RICHARDSON: I saw this boy once and also saw his blood smear. I might mention that he had a normal or nearly normal red-cell count but a marked hypochromic picture due to blood loss. The hemoglobin must have been low. The polymorphonuclear cells contained toxic granulations, a picture frequently seen in severe ulcerative colitis,

which suggests that the disease is of infectious origin.

DR. ERICH LINDEMANN: We had this boy for four weeks on the Psychiatric Service. In some patients with ulcerative colitis a reduction in emotional tension has been followed by such an improvement in the colitis that psychiatric work has become an important factor in treatment. This, however, usually happens in patients with relatively well-adjusted personalities from the psychologic point of view who have recently undergone a severe emotional disturbance following a crisis, such as bereavement. This patient showed a long-standing personality disorder, the correction of which would have required a considerable period of intensive psychiatric work. The disease was too advanced for this work to be attempted.

On the other hand, we expected a rather severe emotional reaction to the operation, because the patient was haunted by morbid fears in connection with fantasies about violence and destruction. He anticipated the operation with extreme anxiety. Considerable efforts to reassure him and to prepare him for the operation seemed to have but little effect.

DR. FRANCIS D. MOORE: The consensus of those who took care of this boy was that an immediate ileostomy when he first came in might have resulted in a more satisfactory outcome. It is asking a lot of the Psychiatric Service to take the responsibility for holding up operation; such a decision rests with the Surgical Service, which evidently underestimated the extent of the patient's disease.

I should like to comment on one or two things that were said in the discussion. At the present time, following ileostomy we frequently see patients who do not have an inordinate fluid loss from the stoma. In fact any patient who has severe loss of fluid and electrolytes may have either ulceration in the terminal ileum or partial obstruction; possibly this boy had both. So far as catheterization is concerned, Dr. Pittman is absolutely correct. The fewer foreign bodies put in and out of an ileostomy, the better. This boy's obstructive point seemed to be 10 cm. inside the stoma. He was not in shape to operate on again, and catheterization seemed to be the only way out. So far as the last operation is concerned, the areas of discoloration on the bowel were 1 to 2 cm. in diameter, so that the chance of their being real tubercles was relatively small. It was a "sick-looking" bowel, and I had no idea what underlay the changes in the bowel wall or the peculiar dilated veins in the mesentery. I had never seen the latter before and could find no ready explanation for it.

#### CLINICAL DIAGNOSES

Chronic ulcerative colitis.  
Perforation of ileum.

A flask of a blood culture grew *Staphylococcus albus*. A number of repeat cultures were negative.

An electrocardiogram on the third day showed a PR interval of 0.15 second, upright but low T<sub>1</sub> and T<sub>2</sub> and a diphaseic T<sub>3</sub>.

The temperature spiked to 103°F. during the first four hospital days. It was then nearly normal for four days, only to be followed by four more days of spiking between 98 and 105°F. It returned to normal again twenty-four hours after the onset of intramuscular penicillin therapy. He had several episodes of diarrhea and vomiting during the first week. These did not recur after aspirin was withheld.

During the second week the spleen appeared larger, and definite lymphadenopathy was noted. The protein had fallen to 4.4 gm. per 100 cc., with an albumin-globulin ratio of 1.2. On the fifteenth day the patient developed slight jaundice. The van den Bergh reaction was 3.4 mg. per 100 cc. direct and 4.6 mg. indirect. The jaundice, fever, joint pains and splenomegaly definitely improved after the fifteenth day. The prothrombin time, the leukocytosis, the sedimentation rate and the van den Bergh reaction also improved gradually during the third and fourth weeks in the hospital. The anemia persisted and the serum protein did not rise above 4.5 gm. The patient had some edema.

After a month in the hospital the patient was discharged to his home, apparently well except for slight pain in the left shoulder.

*Second admission* (three weeks later). During these three weeks he had had a constant cold and sore throat. One week after discharge the shoulders, elbows, hips and knees again became stiff and painful. A week later he developed chest pain, which was severest substernally but shifted from side to side and occasionally extended through to the back. This pain was partially relieved by belching. During the week before admission he vomited almost daily and had severe orthopnea and slight fever. He had had no cough or ankle edema.

Physical examination revealed the patient to be pale and emaciated. The heart and lungs appeared unchanged. The left elbow was swollen and fluctuant. The right elbow and both knees were swollen. There was slight tenderness in the left lumbar region.

The temperature was 100°F., the pulse 120, and the respirations 24. The blood pressure was 100 systolic, 70 diastolic.

During the five weeks spent in the hospital the urine and blood picture remained constant. The urine had specific gravity that was never above 1.008 and gave a ++ test for albumin; the sediment contained an occasional hyaline cast and red cell and 5 white cells per high-power field.

The white-cell count varied from 15,000 to 22,000, with about 80 per cent neutrophils. The hemoglobin remained between 7 and 10 gm. per 100 cc. The smear appeared normal. The sedimentation

rate averaged over 3 mm. per minute but returned to normal in four weeks. The serum nonprotein nitrogen was 36 mg. per 100 cc., and the protein 5.8 gm., with an albumin-globulin ratio of 0.78. The prothrombin time was 27 seconds (normal, 18 to 20 seconds), and the cholesterol 258 mg. per 100 cc. Urine and blood cultures were negative.

The temperature spiked to 102.5°F. for three days after admission, after which it rarely rose above 99.

X-ray examination of the bones of the shoulders showed decalcification, the auricular surfaces of the humeri were somewhat irregular, and there seemed to be subcortical absorption of bone.

Although the joint pains and leukocytosis persisted he was discharged to his home for further bed rest and physical therapy.

*Final admission* (four days later). On the day after discharge he had transient episodes of irrationality and, on the following day, became dyspneic while lying in bed. His physician gave him codeine for joint pain and left pleuritic pain. On the fourth day at 9 a.m. he could not be roused and was readmitted.

Physical examination revealed a pale, thin, dehydrated man. He could be aroused only by painful stimuli. The eyeballs were soft. The neck was not stiff, and a bilateral Hoffmann's sign was elicited. The heart was regular, with a rate of 100.

The temperature was subnormal, and the respirations 16. The blood pressure was 110 systolic, 45 diastolic.

The lungs soon became filled with moist rales and the blood pressure fell to 80 systolic, 20 diastolic. The urine gave a ++++ test for albumin and had a pH of 5.5 and a specific gravity of 1.012. The white-cell count was 30,000, with 90 per cent neutrophils. The serum nonprotein nitrogen was 180 mg. per 100 cc.

The patient became progressively more dyspneic and cyanotic. There were fibrillary twitchings over the body, and he expired about twelve hours after admission.

#### DIFFERENTIAL DIAGNOSIS

DR. WILLIAM W. BECKMAN: On first glance at this record, one thinks of a bacterial infection of some sort. The patient had fever, malaise, weight loss, a markedly elevated white-cell count and an elevated sedimentation rate. These are the clinical features of bacterial infection. If it were an infection it was of several months' duration. This fact alone, with the cardiac findings and the past history of joint disease, makes one wonder about subacute bacterial endocarditis. In spite of all this evidence I have come to the conclusion that this was not a bacterial infection. In the first place, he was a young man who had had several previous attacks of joint disease and whose present illness was again characterized by joint symptoms in addition to the constitutional manifestations.

ing ileostomy; as Dr. Moore has suggested, this disease in the ileum may have been due to a partial obstruction. Dr. McKittrick, after hearing the results of this case, said that he recalled one other case in which a similar ileitis had occurred following obstruction in the ileum; he wondered whether this ileitis might have resulted from obstruction. You did not find obstruction in the ileum at the time of operation, Dr. Moore? Perhaps there was some other factor, but the fact that the distal loop was not involved suggests that it may have been the mechanical factor of obstruction that contributed some way in the development of this severe acute ulcerative ileitis and death.

DR. MOORE: We did not find obstruction, and yet, as has been pointed out in these meetings before, obstruction of an ileostomy can be due to the interaction of two factors—the caliber of the ileostomy and the propulsive force of the bowel behind it. With even a normal ileostomy stoma, a proximal bowel with deficiency disease cannot push the fecal stream through.

DR. RICHARDSON: What happens is that a lot of digestive juice does not reach the distal ileum. One of the surprising things about human beings is that they do not “eat up their own guts,” so to speak. I think that it may be a factor in cases of ulcerative colitis.

DR. PITTMAN: What about catheterization? Was there really a stenosis of the stoma, and could there have been enough trauma to cause the perforation?

DR. MOORE: The patient died in two hours, obviously from a perforation of a hollow viscus. We were afraid of catheter trauma, but these lesions were about 150 cm. above the stoma.

## CASE 31212

### PRESENTATION OF CASE

*First admission.* A twenty-one-year-old machinist was admitted to the hospital with fever, precordial discomfort and inflamed joints.

At the age of eight he had chills and fever and developed warm and red joints and masses on the back of his hands. He was not asymptomatic until the following summer, about eight months later. During the next winter the same illness recurred with fever and warm, swollen, red joints. The joints of the hands were exquisitely tender. He spent that winter in a hospital, where splints were used to correct flexion deformities of the fingers. The following spring his joints suddenly and spontaneously improved, and he walked for the first time in six months. He was said to have no involvement of the heart. Four years later, he had another severe recurrence. He spent almost a year in bed, and he was soon free of symptoms and deformities. He subsequently attended a trade school

for a year, and three years before admission he began to work as a machinist. Until the present illness he had been well and had worked sixty hours each week in a shop. Four weeks before entry he awoke with a sense of precordial and substernal pressure aggravated by deep breathing. A headache was somewhat relieved by elevating the head on four or five pillows. He also began to note considerable malaise. Five days later the temperature was 99.8°F., and it had remained elevated until admission. An electrocardiogram at that time was said to have indicated that he had a “wicked heart.” About three weeks before entry the elbows, shoulders and knees became stiff and tender. At about that time the throat became sore. A week later a physician noted pink spots on the toes. Two or three days before admission he had periumbilical abdominal cramps. On the day before admission he had several more such attacks, accompanied by vomiting and diarrhea. He had lost an unknown amount of weight.

He had drunk three or four bottles of beer and three or four “shots” of whisky every day. He had never had scarlet fever.

Physical examination showed a man with hot moist skin, appearing extremely ill. The heart was 10 cm. to the left of the midsternum in the sixth interspace. There was a regular rate of 110. A mitral diastolic rumble with a presystolic accentuation was thought to be heard. The lungs were clear. The liver was not considered to be significantly enlarged but there was definite tenderness in the region of the liver. The tip of the spleen was palpable on inspiration. The fingers, wrists, elbows and shoulders were painful, tender and stiff. There were several reddish-brown spots, suggestive of petechiae, on the dorsum of the left great toe.

The temperature rapidly rose from 101 to 104.4°F., and the pulse from 90 to 120. The respirations were 20. The blood pressure was 130 systolic, 65 diastolic.

The urine was light amber, cloudy and acid in reaction, with a specific gravity of 1.004 and a +++ test for albumin; the sediment contained 3 white cells per high-power field. There was no sugar, diacetic acid or bile.

Examination of the blood showed a white-cell count of 18,600, with 87 per cent neutrophils and 8 per cent lymphocytes. The hemoglobin was 9.8 gm. per 100 cc. A blood Hinton test was negative. A stool was green and formed; it was guaiac negative. The sedimentation rate was over 2 mm. per minute. The serum nonprotein nitrogen was 34 mg. per 100 cc., the protein 6.1 gm., and the cholesterol 195.0 mg. The chloride was 91 milliequiv. per liter. A van den Bergh test was negative. The prothrombin time was 54 seconds (normal, 18 to 20 seconds). A cephalin flocculation test was + in forty-eight hours. Agglutination tests for typhoid, paratyphoid and undulant fevers were negative. One

sary criteria for the diagnosis of rheumatoid arthritis. The description of the second and third attacks is quite clearly that of Still's disease. I do not believe that anyone would have had difficulty in making the diagnosis. The child was extremely sick, with fever and weight loss. Joint deformities developed that required straightening by means of splints. This is an almost unheard of train of events in rheumatic fever. Furthermore, the present joint manifestations sound classic for rheumatoid arthritis, and the x-ray films, as they are described, are also classic for rheumatoid arthritis. The films of the shoulders are all that we need to see.

DR. MILFORD D. SCHULZ: This film of the left shoulder shows subchondral decalcification and irregularity of the subchondral bone.

DR. BECKMAN: The x-ray film is characteristic of rheumatoid arthritis and, coupled with the clinical course of this attack and the previous ones, makes that diagnosis mandatory. The fever, leukocytosis, anemia, splenomegaly, lymphadenopathy and elevated sedimentation rate are all often seen in rheumatoid arthritis.

Rheumatic heart disease has frequently been found in post-mortem examinations of patients with unquestionable rheumatoid arthritis.<sup>1, 2</sup> This always raises the unanswerable question. Were the patients suffering from both rheumatoid arthritis and rheumatic fever or from a single process that produced both joint and heart lesions? I am confused about whether the characteristic cardiac findings of rheumatic fever were present in this case, and I shall have to have Dr. Castleman tell me. The typical murmur of mitral stenosis was "thought to be heard" on admission, but in all the subsequent physical examinations the heart was described as "the same." Was there evidence of heart disease?

DR. CASTLEMAN: Dr. Lerman, can you answer that?

DR. JACOB LERMAN: I should say that he did not have evidence of rheumatic heart disease.

DR. BECKMAN: I wondered, because it is difficult to interpret "thought to be."

We apparently do not have to consider rheumatic fever. The marked renal disease, however, cannot be explained by rheumatoid arthritis and suggests another member of "The Group," — lupus erythematosus, — which is characterized by splenomegaly, lymphadenopathy, serous-membrane involvement, fever and renal disease as extensive as this, leading to a nephrotic-like picture and to death. One can categorically say, however, that this patient did not have lupus erythematosus because he did not have the characteristic skin lesions and leukopenia, both of which are essential features of the illness. But the kidney picture does suggest it. Periarthritis nodosa, another member of "The Group" also produces renal disease. It is a generalized vascular disease and as a clinical entity it is characterized by evidence of vascular disturbances,

such as angina pectoris, cerebral accidents, mesenteric thrombosis and so forth. It may occur, however, in association with other members of "The Group." This was eloquently pointed out in 1938 by Dr. Soma Weiss<sup>3</sup> in the discussion of a case of clear-cut disseminated lupus erythematosus. It appears to be, as indeed do all the members of "The Group," a response of the body to a variety of stimuli.

The lesions of periarthritis nodosa have been observed in patients suffering from serum sickness and also in patients suffering from sulfonamide intoxication. They have been produced experimentally in animals by the injection of certain fractions of human serum protein. The frequent association of this type of vascular change with the other members of "The Group" makes it likely that the renal disease was on the basis of periarthritis nodosa. Of course I have no way of ruling out an independent lipoid nephrosis or chronic glomerulonephritis, but as I have said, I should prefer to explain all the features of this illness on a single disease process. We also have to consider the possibility of amyloid disease in association with rheumatoid arthritis. This occurs not infrequently. Amyloid disease, however, is usually observed in cases of long duration, and even though I believe that the same process had been present since the first attack, at the age of eight, it is unlikely that amyloid disease developed in this case, because of the eight years of complete freedom of symptoms that he had had before the onset of the present attack.

A word about the liver disease — that also, we think, can be associated with rheumatoid arthritis. We have been studying liver function in patients with rheumatoid arthritis and have been surprised at how many have had one or two disturbed liver-function tests. We have had several autopsies in this hospital on cases of "The Group" in which definite pathological evidence of liver disease was found.

The terminal episode was uremia, although one cannot rule out a vascular accident. It might have been the latter, for it was rather abrupt. This is further evidence of periarthritis nodosa. I shall sum up by saying that the disease lies in the group of syndromes that I have discussed, the likeliest one being rheumatoid arthritis, with features of several of the other members, and that the renal lesions were due to periarthritis nodosa.

DR. LERMAN: I have mentioned the fact that this patient did not have rheumatic heart disease. When he first came in we thought that the underlying disease was subacute bacterial endocarditis, in spite of the fact that the normal state of his heart was against it. We watched him for ten days, and the temperature continued to spike up to 105°F. In fact we were sure that he was going to die. As a last resort we tried penicillin, and the response was dramatic. The temperature fell to normal on the



Therefore, one would like to relate the present illness to the previous ones and to consider it as being an exacerbation of some fundamental process. If the previous attacks of joint disease had been more clearly like rheumatic fever one could relate them, by saying that he had rheumatic heart disease and a superimposed subacute bacterial endocarditis. But actually the description, at least that of the second and the third attack, is not that of rheumatic fever, because he had definite joint deformities of long duration that required orthopedic correction. My conception of rheumatic fever visualizes acute joints, without marked deformity, which rarely if ever become chronic, whereas I believe that the description of the earlier illnesses is exactly what would be expected in rheumatoid arthritis. Another point against any kind of infection is the negative bacteriology throughout the course of the illness. No one knows from the record how many blood cultures were taken but certainly there must have been a great number during the first and second admissions. On one occasion *Staph. albus* grew in one flask, but that can safely be put down as a contaminant. The so-called "response" to penicillin does not appear to have been a true response, and this is further evidence that there was not a bacterial organism susceptible to penicillin. When the fever came down, it looked like a wonderful response, but the same thing had occurred spontaneously eight days before, without penicillin. In spite of the fact that the fever came down, it is obvious that the fundamental process did not improve in any way. He continued to have leukocytosis, an elevated sedimentation rate and joint pains, as well as all the other symptoms of his illness. Therefore I do not believe that it can be called a response.

I should like to know what it means when it says that the tests improved. Does it mean that they were normal or merely went in the direction of normal after penicillin?

DR. BENJAMIN CASTLEMAN: Dr. Berg, can you tell us about that?

DR. ROBERT L. BERG: The van den Bergh test was too low to read, and most of the other tests became more nearly normal. The sedimentation rate, however, remained elevated.

DR. MARIAN W. ROPES: So did the white-cell count.

DR. BECKMAN: The fact that the tests did not return to normal, although they went in the direction of normal, provides further evidence that penicillin did not fundamentally affect the course of the illness. This militates against the diagnosis of subacute bacterial endocarditis.

He had spots on his toes that resembled petechiae, but in subacute bacterial endocarditis of three months' duration I should expect a great deal more evidence of embolic phenomena. Focal emboli to the kidney might explain the albuminuria, but if that were the case a fluctuating urinary picture with

showers of red cells would have been found, rather than a constant one without red cells. It expressly states in the record that the urinary findings were constant. An enlarged spleen can go with bacterial endocarditis, but splenomegaly is by no means diagnostic of this or any disease.

On the basis of these considerations I decided that this man did not have a significant bacterial infection. If any was found at autopsy it probably represents a terminal event that had no particular relation to the course of the total illness.

My ideas about the fundamental process in this case are rather difficult to express. Although I shall not be able to make a single diagnosis that will explain all the signs and symptoms, I believe that he was suffering from a single disease process and that that process can be classified as a member of the group of related syndromes that includes rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, dermatomyositis, periarteritis nodosa and so forth. These diseases or syndromes are similar in that they all have marked constitutional symptoms, such as excessive fatigability, weight loss and cold sweating hands and feet. The courses of all of them may be punctuated by fever, although this is less frequent in rheumatoid arthritis. Joint signs and symptoms of varying degree are common to all. Except in lupus erythematosus disseminatus, leukocytosis may be present.

In addition to all these things that are common to the entire group, each member has features not present in the related conditions that dignify it as a syndrome. Rheumatoid arthritis, for example, is characterized by deformed joints, with both x-ray and pathological evidence of bone and joint destruction, whereas rheumatic fever shows characteristic heart involvement. That is to say, there is something in the straight clear-cut syndrome of rheumatoid arthritis that is not present in the syndrome of rheumatic fever, lupus erythematosus or any of the others. The same can be said for each of these related syndromes. Many names have been suggested for this large aggregate of related diseases. Such terms as generalized constitutional disease, generalized connective-tissue disease, mesenchymal disease, generalized vascular disease and neurovascular disease have been employed by various authors. Any one of them, however, is much too limited in scope to describe adequately the widespread nature of this group of diseases. For want of a better name we in the Arthritis Clinic of this hospital have adopted the convention of calling them "The Group." We continue to search for an adequate name and welcome suggestions.

Another reason we believe that these conditions are related is that not infrequently one encounters in a single patient at a given time the characteristic features of two or more of these syndromes. This is well exemplified by this case. In the first place, I think there can be no doubt that he had the neces-

sary criteria for the diagnosis of rheumatoid arthritis. The description of the second and third attacks is quite clearly that of Still's disease. I do not believe that anyone would have had difficulty in making the diagnosis. The child was extremely sick, with fever and weight loss. Joint deformities developed that required straightening by means of splints. This is an almost unheard of train of events in rheumatic fever. Furthermore, the present joint manifestations sound classic for rheumatoid arthritis, and the x-ray films, as they are described, are also classic for rheumatoid arthritis. The films of the shoulders are all that we need to see.

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DR. JACOB LERMAN: I should say that he did not have evidence of rheumatic heart disease.

DR. BECKMAN: I wondered, because it is difficult to interpret "thought to be."

We apparently do not have to consider rheumatic fever. The marked renal disease, however, cannot be explained by rheumatoid arthritis and suggests another member of "The Group," — lupus erythematosus, — which is characterized by splenomegaly, lymphadenopathy, serous-membrane involvement, fever and renal disease as extensive as this, leading to a nephrotic-like picture and to death. One can categorically say, however, that this patient did not have lupus erythematosus because he did not have the characteristic skin lesions and leukopenia, both of which are essential features of the illness. But the kidney picture does suggest it. Periarteritis nodosa, another member of "The Group" also produces renal disease. It is a generalized vascular disease and as a clinical entity it is characterized by evidence of vascular disturbances,

such as angina pectoris, cerebral accidents, mesenteric thrombosis and so forth. It may occur, however, in association with other members of "The Group." This was eloquently pointed out in 1938 by Dr. Soma Weiss<sup>3</sup> in the discussion of a case of clear-cut disseminated lupus erythematosus. It appears to be, as indeed do all the members of "The Group," a response of the body to a variety of stimuli.

The lesions of periarteritis nodosa have been observed in patients suffering from serum sickness and also in patients suffering from sulfonamide intoxication. They have been produced experimentally in animals by the injection of certain fractions of human serum protein. The frequent association of this type of vascular change with the other members of "The Group" makes it likely that the renal disease was on the basis of periarteritis nodosa. Of course I have no way of ruling out an independent lipoid nephrosis or chronic glomerulonephritis, but as I have said, I should prefer to explain all the features of this illness on a single disease process. We also have to consider the possibility of amyloid disease in association with rheumatoid arthritis. This occurs not infrequently. Amyloid disease, however, is usually observed in cases of long duration, and even though I believe that the same process had been present since the first attack, at the age of eight, it is unlikely that amyloid disease developed in this case, because of the eight years of complete freedom of symptoms that he had had before the onset of the present attack.

A word about the liver disease — that also, we think, can be associated with rheumatoid arthritis. We have been studying liver function in patients with rheumatoid arthritis and have been surprised at how many have had one or two disturbed liver-function tests. We have had several autopsies in this hospital on cases of "The Group" in which definite pathological evidence of liver disease was found.

The terminal episode was uremia, although one cannot rule out a vascular accident. It might have been the latter, for it was rather abrupt. This is further evidence of periarteritis nodosa. I shall sum up by saying that the disease is in the group of syndromes that I have discussed, the closest one being rheumatoid arthritis, with features of several of the other members and that the renal lesions were due to periarteritis nodosa.

DR. LERMAN: I have mentioned the fact that this patient did not have rheumatoid heart disease. When he first came in we thought that the heart disease was rheumatic heart disease, in spite of the fact that the serum was negative, and was against it. We wanted to see if the patient was going to die. As a matter of fact, he came to die. As a matter of fact, the response was that the temperature fell to normal on the

second day. Not only was there an improvement in temperature, but his clinical condition also improved. Everyone who saw him agreed that he had made a good response to penicillin. A course of penicillin at the time of his second admission also caused improvement, but the response was not too definite. After a period of time he was able to go home.

DR. J. H. MEANS: I saw this man half an hour before he died and refrained from making a diagnosis, although I did make a correct prognosis. I did not believe that he had subacute bacterial endocarditis, although I thought that it was a possibility. I thought that he had more than uremia to account for his death, and I wondered whether he had had a cerebral vascular accident as a terminal episode.

DR. ROPES: In regard to the response to penicillin, it is true that he improved clinically, but to me at least, it was not a real response because the laboratory signs of activity persisted and the leukocytosis continued to be 18,000 to 20,000 after one of the courses of treatment. In addition, we often see a similar course in this group of diseases without the use of penicillin. In lupus erythematosus and less frequently in rheumatoid arthritis, we frequently observe this picture—a high fever that appears suddenly, lasts a few days and then disappears. During that period the patients often appear moribund and yet recover. In such cases the question often arises whether or not they should receive sulfonamides. In some of them we have thought that the giving of sulfonamides led to death. We did not have that problem in this patient, however, since there is no evidence that penicillin causes similar bad results in patients with these diseases.

#### CLINICAL DIAGNOSES

Lupus erythematosus disseminatus?  
Subacute bacterial endocarditis?  
Uremia.

#### DR. BECKMAN'S DIAGNOSES

Rheumatoid arthritis.  
Periarteritis nodosa, involving the kidney.

#### ANATOMICAL DIAGNOSES

Rheumatoid arthritis.  
Amyloidosis of kidneys, spleen and liver.  
(Uremia.)  
Polyserositis, hemorrhagic.  
Bronchopneumonia.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy showed about 250 cc. of clotted blood in each pleural cavity. We found the same amount of blood in the abdominal cavity but no signs of peritonitis. The heart was normal in size; but on the epicardial surface was a loose, ad-

herent gelatinous material producing interadherence between the parietal and the visceral pericardium. Sections of the pericardium showed microscopically numerous polymorphonuclear cells and fibrin, suggesting an acute or subacute pericarditis. The same reaction was present on the pleura and peritoneum. There was therefore a hemorrhagic polyserositis. The valves of the heart were normal. There was no evidence of rheumatic heart disease, and no thrombi on any of the valves to suggest a nonbacterial thrombotic endocarditis, such as one sometimes sees with lupus erythematosus.

The kidneys were the striking feature of this autopsy. They weighed 600 gm. together, and were quite hard and white. In the gross the condition almost suggested lymphomatous infiltration. Microscopically this whitish infiltration proved to be an extensive amyloid degeneration. Practically every glomerulus and vessel were involved. No wire-loop lesions, which are often seen in cases of lupus erythematosus, were observed. The amyloidosis was corroborated by the findings in the spleen, which weighed 450 gm. and had what is often called a "sago" appearance. Microscopically all the vessels in the centers of the Malpighian corpuscles showed marked amyloid degeneration of their walls.

DR. ROPES: We were unable to examine the joints but did get fluid from the shoulder joint, which contained approximately 70,000 white cells of which 85 per cent were polymorphonuclear cells, and there was also a great deal of what must be called cellular debris, similar to the material we see in cases of rheumatoid arthritis of long duration, where there is a great deal of tissue destruction.

DR. CASTLEMAN: We inoculated the material into various aerobic and anaerobic mediums but were unable to obtain any growth. The blood culture was also negative. I believe that there is little doubt that the joint disease was rheumatoid arthritis.

DR. ROPES: The fluid sugar was high, which one does not find usually with infectious arthritis even following intravenous glucose administration.

DR. CASTLEMAN: I do not believe that the joint lesions were infectious. The patient did have a terminal bronchopneumonia. I still do not understand why there was frank blood in the pleura and peritoneum.

DR. LERMAN: Could it have been associated with the uremia?

DR. BECKMAN: Pleural and pericardial involvement is not infrequent in rheumatoid arthritis.

DR. ALLAN M. BUTLER: How common is amyloid disease in rheumatoid arthritis?

DR. ROPES: It varies; in some small series of Still's disease it has been reported as high as 50 per cent. It has not usually been reported so high as that in this country, and in our group it is relatively low—below 10 per cent. We have had several patients with amyloid disease but the usual

course is a slow downhill one with gradually increasing renal failure.

It is interesting that Carroll and Nelson<sup>4</sup> have reported a case of rheumatoid arthritis with amyloidosis in which the patient died with hemorrhage in the abdomen.

DR. LERMAN: It is a general principle that new therapeutic agents bring about new clinical pictures as complications or sequelae. For example, thioracil causes agranulocytosis, characteristic febrile reactions and adenopathy. The sulfonamides cause a characteristic nephritis. I should like to offer the suggestion that this type of case represents the sequence of events that may follow the use of penicillin and that such cases may occur regularly in the future. Let us assume that this patient had a history of rheumatic disease fifteen years previously. This may have been rheumatic fever or rheumatoid arthritis. He develops a fulminating infection that

behaves in some respects like subacute bacterial endocarditis or septicemia. Penicillin produces a dramatic recovery. The bacteria, however, are not licked — they go underground. The serous cavities are a good hideout, and the infection smolders along there without any serious systemic reaction. Death finally results, not from the infection but from a degenerative process caused by chronic suppuration. An analogous sequence of events takes place in chronic osteomyelitis.

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with a determination that we will not so easily forget again.

We must remember the soil that will be forever reddened with the blood of young Americans — at Kasserine Pass and over the hills that fall away to Tunis and Bizerte, in Sicily and at Salerno, at Benevento and Cassino, in the cockpit of Anzio and up the bony ridge of Italy, on the beaches and across the fields of France, and on the plains and by the rivers of Germany.

We must bear in mind certain words that have become part of our spiritual bill of rights — "That from these honored dead we take increased devotion to that cause for which they here gave the last full measure of devotion; that we here highly resolve that these dead shall not have died in vain; that the nation shall, under God, have a new birth of freedom. . . ."

We must remember a new lesson, phrased by Norman Corwin in words written apropos of this event that we now commemorate — "We've learned that freedom isn't something to be won and then forgotten. It must be renewed, like soil after yielding good crops; must be rewound, like a faithful clock; exercised, like a healthy muscle."

And still we must remember that another victory is yet to be won, our power redeployed, another mile traversed, however long, before we can devote ourselves fully to the problems of a peace so hardly won.

## VICTORY IN EUROPE

IT SEEMS particularly fitting that our day of victory in Europe should have come in May, for May is the month that we long ago selected in which to have our day of remembrance, and there is much that we must not forget.

We must not forget our grim horror at the tales of Buchenwald, Nordhausen, Belsen and Erla, at prisoners of war murdered in the snow, at unrestricted U-boat sinkings, at Coventry and at the blind rage of rocket bombs. We must remember these things, not with hate, but with a long memory that can outlive the passing of events. We must remember the forgetfulness of the years after 1918,

## THE CASE AGAINST FRIED FOODS

AS LONG ago as February, 1944, Dr. Frank Howard Richardson<sup>1</sup> published in the *Journal of Pediatrics* the results of his ardent researches into the digestibility of fried foods. Up to that time it had been assumed, and in those quarters unacquainted with his conclusions it still is assumed, that fried foods are harmful, especially for children. With wartime shortages particularly in mind, Dr. Richardson thought that the soundness of our dietary beliefs should be investigated.

Three sources of authority were open — published records of research, current books and bulletins, and the opinions of living experts in the fields of

nutrition and pediatrics. Surprisingly, only one piece of published research was revealed, and that nearly seventeen years older than the present study. In 1927, Boggess and Ivy<sup>2</sup> had investigated, on dogs and human beings, the digestibility of potatoes prepared after various culinary patterns. According to their conclusions, the starch of the pan-fried potato is more easily digested than that of the French-fried, and that of the French-fried more easily than that of the boiled specimen. Fat, it was found, actually facilitated the rate of digestion, determined by fluoroscopic observations.

Dr. Richardson found that authoritative textbooks on nutrition, federal and state health bulletins, pamphlets on child care and so forth almost universally condemned all foods prepared after the fashion that made famous, if not popular, the sixth day of the week. No scientific proof was presented for these pontifical opinions: fat may be an excellent food principle, but not the foods that are cooked in it. So far as these tribunals are concerned, the only edible part of the doughnut is the hole. "In frying," according to one of these witnesses, "decomposition products are formed, which are irritating to the digestive tract." And that was that.

Various specialists were then consulted — eleven nutritionists, biochemists and physiologists, seven pediatricians of national reputation, two pediatricians high in the Children's Bureau, two gastroenterologists, one nutrition director of the American Red Cross, two medical editors and two research-bureau heads. Not one of these authorities let the investigator down. The cruelest indictment of fried foods was that overindulgence might be unwise; a differentiation was also made of fried foods properly cooked and those that were simply soaked in hot fat.

And so at last comes vindication, permanent we trust, for the fried spud, the flapjack and the doughnut, the crisp egg — sunny side up or, in the vernacular, "one eye open" — and the Sunday-morning fishball.

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## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**BATTERSHALL** — Jesse W. Battershall, M.D., of Attleboro died May 4. He was in his fifty-second year.

Dr. Battershall received his degree from Tufts College Medical School in 1916. He had served as medical examiner in Bristol North district for twenty years and as school physician in Attleboro for twenty-three years. In 1943 he was named municipal health officer. He was a member of the Sturdy Memorial Hospital staff.

His widow survives.

**LEIB** — Edwin R. Leib, M.D., of Worcester, died May 5. He was in his seventy-first year.

Dr. Leib received his degree from Boston University School of Medicine in 1899. He retired as chief of the medical service at Hahnemann Hospital a few months ago but remained on the staff as a consultant. He was also a consultant on the Belmont Hospital staff. For more than thirty years, Dr. Leib had served as epidemiologist in the Worcester Health Department. He was president of the Worcester Blood Bank.

His memberships included the Worcester District Medical Society of which he was past president, as well as a councilor at the time of his death. He was a fellow of the American Medical Association.

His widow and a brother survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### COMMUNICABLE DISEASES IN MASSACHUSETTS FOR APRIL, 1945

DISEASES	RÉSUMÉ		
	APRIL 1945	APRIL 1944	SEVEN-YEAR MEDIAN
Anterior poliomyelitis	2	1	1
Chancroid	2	1	*
Chicken pox	964	2791	1286
Diphtheria	24	18	13
Dog bite	1317	908	945
Dysentery, bacillary	0	0	7
German measles	195	398	398
Gonorrhea	461	319	355
Granuloma inguinale	0	0	*
Lymphogranuloma venereum	2	7	*
Malaria	124	53	2
Measles	732	3491	4012
Meningitis, meningococcal	21	40	7
Meningitis, Pfeiffer-bacillus	2	5	1
Meningitis, pneumococcal	7	9	4†
Meningitis, staphylococcal	0	1	0†
Meningitis, streptococcal	0	2	1†
Meningitis, other forms	2	0	2†
Meningitis, undetermined	2	13	8†
Mumps	2431	1483	1109
Pneumonia, lobar	322	350	390
Salmonella infections	6	5	5
Scarlet fever	1428	1724	1641
Syphilis	342	334	455
Tuberculosis, pulmonary	219	179	232
Tuberculosis, other forms	7	18	19
Typhoid fever	2	4	3
Undulant fever	2	3	3
Whooping cough	568	313	625

\*Made reportable in December, 1943.

†Four-year average.

### COMMENT

Diphtheria is still at a high point — the highest April for the last ten years. This year's April figure of 24, however, is far below those of Aprils previous to 1935.

Meningococcal meningitis remained well above the seven-year median. It should be remembered, however, that the figures on which this seven-year median was based include several Aprils with extremely low incidences.

Mumps was very prevalent but is beginning to show the usual seasonal decline.

Measles continues at an extremely low point.

All the cases of malaria originated outside the United States.

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

- Anterior poliomyelitis was reported from: Boston, 2; total, 2.
- Diphtheria was reported from: Boston, 8; Brockton, 1; Camp Edwards, 2; Everett, 1; Falmouth, 1; Hingham, 1; Lawrence, 1; Lowell, 3; Lynn, 1; New Bedford, 2; Revere, 1; Somerville, 1; Worcester, 1; total, 24.
- Encephalitis, infectious, was reported from: Lexington, 1; total, 1.
- Malaria was reported from: Boston, 2; Camp Edwards, 75; Cushing General Hospital, 9; Everett, 1; Natick, 1; Northampton (U. S. Veterans Hospital), 1; Quincy, 1; Regional Hospital (Waltham), 33; Springfield, 1; total, 124.
- Meningitis, meningococcal, was reported from: Boston, 6; Easthampton, 1; Everett, 1; Haverhill, 1; Hingham, 1; Middleboro, 1; Quincy, 1; South Hadley, 1; Springfield, 4; Stoughton, 1; Sturbridge, 1; Walpole, 1; West Springfield, 1; total, 21.
- Meningitis, Pfeiffer-bacillus, was reported from: Boston, 1; Lawrence, 1; total, 2.
- Meningitis, pneumococcal, was reported from: Boston, 3; Cambridge, 1; Fall River, 1; New Bedford, 1; Reading, 1; total, 7.
- Meningitis, other forms, was reported from: Boston, 1; Weymouth, 1; total, 2.
- Meningitis, undetermined, was reported from: Boston, 1; Springfield, 1; total, 2.
- Salmonella infections were reported from: Boston, 2; Lawrence, 3; Newton, 1; total, 6.
- Septic sore throat was reported from: Boston, 10; Brookline, 1; Cambridge, 1; Haverhill, 1; Lynn, 1; Merrimac, 2; Milton, 1; North Adams, 1; Pittsfield, 1; total, 19.
- Tetanus was reported from: Cambridge, 1; Kingston, 1; total, 2.
- Trichinosis was reported from: Boston, 3; Fall River, 1; total, 4.
- Typhoid fever was reported from: New Bedford, 1; South Hadley, 1; total, 2.
- Undulant fever was reported from: Northampton, 1; Southbridge, 1; total, 2.
- Weil's disease was reported from: Ware, 1; total, 1.

## BOOK REVIEWS

*Gastro-Enterology* (three volumes). By Henry L. Bockus. Vol. II. *The Small and Large Intestine and Peritoneum: Diagnosis and Treatment of Disorders of the Small Intestine, Colon, Peritoneum, Mesentery and Omentum*. 4<sup>th</sup>, cloth, 975 pp., with 311 illustrations and 53 tables. Philadelphia and London: W. B. Saunders Company, 1944. \$12.00.

This is an excellent book, half of which was written by Dr. Bockus and half by his colleagues in the Graduate Hospital of the University of Pennsylvania. It is easily the best textbook on the subject in English in the past twenty-five years, and fills a real need. The style is pleasing, and the book is well printed and bound and beautifully and copiously illustrated. At the beginning of each chapter there is an index of contents, and a well-chosen list of references is supplied at the end. About one third of the book covers the small intestine, and nearly two thirds considers the large intestine, with the remainder — about fifty pages — on the peritoneum, mesentery and omentum. The material is so varied and extensive that it is hard to single out special chapters for review.

One has only to compare this volume with the standard textbooks of twenty years ago to note the great progress that has been made in the diagnosis and treatment of diseases of the intestine — the free use of the roentgen ray, the use of the Miller-Abbott tube in intestinal obstruction, the better classification of diarrheas, the complete description of ileitis, the use of vitamins, the medical treatment of megacolon, the absence of the usual hundred-page chapter on "intestinal intoxication," and the changes in operability and surgical mortality.

The radiographic illustrations are clear and easy to understand. The color films taken through the proctoscope are really remarkable. The value of examination of the feces is clearly shown. A fuller discussion of peritoneoscopy is promised in the third volume. The description of rectosigmoidoscopy is complete and satisfactory. As is the examination of the feces on an ordinary or a Schmidt test diet, and the use

of barium enemas. The discussions of fluid and salt needs in patients with diarrhea, vomiting and gastrointestinal aspirations are valuable.

The chapter on intestinal obstruction is one of the largest in the book, modern methods of diagnosis and treatment being fully outlined. In the chapter on ileitis the whole subject is brought up to date and is especially well illustrated, and the symptoms and indications for medical and surgical treatment are clear. Mesenteric embolism and thrombosis seem to have been omitted in the differential diagnosis of the acute abdomen, and the value of the urinary diastase level in such cases should be stressed. In the chapter on intestinal carbohydrate dyspepsia, it is surprising that Schmidt and Strassburger, who named and first described the disease in 1901, are not mentioned.

Developmental anomalies of the colon — high and low cecum, redundant colon and so forth — are conservatively dealt with. Modern methods of medical and surgical treatment of megacolon are well outlined. The discussion of the etiology and treatment of one obscure disease, chronic ulcerative colitis, is especially good. The statement that symptoms are present in over 50 per cent of cases of noncomplicated diverticulosis of the intestine seems odd, and suggests that patients with diverticula who have no gastrointestinal symptoms and no roentgenologic examination are not included. The chapters on tumors and granulomas of the bowel are excellent. Chronic appendicitis is treated conservatively.

Tuberculous peritonitis is given one page in contrast to the twenty pages of the older books, which probably corresponds to its lessened incidence.

This book can be highly recommended to the general practitioner and to the specialist.

*Synopsis of Neuropsychiatry*. By Lowell S. Selling, M.D., Ph.D., Dr.P.H. 12<sup>o</sup>, cloth, 500 pp. St. Louis: C. V. Mosby Company, 1944. \$5.00.

The book is a simplified manual, well arranged and covering the whole field of neurology and psychiatry. The definitions are clear and concise, and the material is set out in an extremely attractive manner, so that a reference may be easily found. The book is obviously by an expert, with full knowledge of the physiology and pathology of the nervous system, as well as a complete grasp of the clinical aspects. In general, the volume is up to date, in spite of the rapid changes in many aspects of the subject in recent years. There is a good index, but no references to the literature. The book may safely be put in the hands of students, nurses and social workers, provided that they realize that some may differ from the author in the small technical points of a controversial nature.

## NOTICES

## GREATER BOSTON MEDICAL SOCIETY

A dinner meeting of the Greater Boston Medical Society will be held in the State Suite of the Copley Plaza on Tuesday, May 29, at 6:30 p.m. Dr. Ernst P. Boas, of New York, will speak on the subject "Medical Care in the Postwar Era."

## BOSTON CITY HOSPITAL ALUMNI ASSOCIATION

There will be a clinical meeting of the Boston City Hospital Alumni Association on Saturday, May 26, at 10:30 a.m. in the Cheever Amphitheater, Dowling Building.

## PROGRAM

The Use of Penicillin Aerosolization in the Treatment of Serious Respiratory Disease. Dr. Maurice S. Segal.  
Strangulated Umbilical Hernia. Dr. William A. White, Jr.  
Primary Cancer of the Lung. Dr. John W. Strieder.  
Penicillin Therapy. Dr. Maxwell Finland.  
Postwar Graduate Medical Training. Dr. Harold J. Jeghers.

Physicians and medical students are invited to attend.

Luncheon for the alumni, as guests of the trustees, will be held in the House Officers' Dining Room at 12:30 o'clock.

(Notices continued on page xv)

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## LIGATION OF THE INFERIOR VENA CAVA IN THE PREVENTION AND TREATMENT OF PULMONARY EMBOLISM\*

E. EVERETT O'NEIL, M.D.†

BOSTON

THE interruption of deep venous pathways in the treatment and prevention of pulmonary embolism has come to be a generally accepted surgical procedure. The preferred sites for division when deep venous thrombosis is present, or when pulmonary infarction has taken place without evident thrombosis but the latter is suspected, have been the superficial femoral veins, the common femoral veins and, in a few cases, the external and common iliac veins. In the majority of cases, section of the above-named vessels has been adequate to prevent further extension of thrombosis, with its possible detachment of a fatal or near-fatal embolus. It must, however, be pointed out that there have been occasions when embolism, in a few cases with a fatal result, has occurred after bilateral division of deep veins. The reasons for such fatalities are not always clear. If one has interrupted a vein at a point where a thrombus was present and is not sure that all clot had been suctioned from the proximal segment, it may well be argued that a possible remaining thrombus can produce a fatal outcome; or if the superficial, and not the common, femoral vessels have been interrupted, one may deduce that a propagating thrombus may develop in the deep femoral vein, with subsequent detachment of a fatal embolus. When, however, the first sign of trouble is a sudden pulmonary episode of mild pleuritic pain, with cough and bloody sputum, suggesting a minor embolic process, and inspection of the lower extremities reveals no evidence of the usual stigmas of deep thrombosis, one may postulate a quiet thrombosis in the deep venous plexus of the legs and feel justified in performing a bilateral division of the femoral veins. Operation may reveal no clot in either vein, and a proper division may be done. Despite this procedure a fatal embolism may occur several hours or days later. The obvious query concerns the source of this embolus, and the method of averting it. It is the purpose of this paper to sug-

gest that, in certain selected cases, it may be pertinent to interrupt the inferior vena cava to circumvent the possibility of just such a catastrophe as has been mentioned. It must be admitted that the indications for the employment of such a procedure are limited; nevertheless, they are extremely important.

There appear to be two distinct indications for ligation of the inferior vena cava that have been encountered in a large series of divisions of deep veins: the first exists when the diagnosis of phlebothrombosis is obvious and the site of the lesion is apparent; the second exists when one or more emboli have occurred but their source is obscure. To elaborate further, in the first type of case a synchronous propagating thrombosis may take place in both legs, and when the condition is first observed the thrombotic processes may have extended to the inguinal ligaments or beyond, with or without the production of pulmonary embolism. As a more frequent finding, instead of simultaneous thrombosis in both lower extremities, a phlebothrombosis may occur in one limb, extending to the groin, the thrombus changing in character with the passage of time from a loose, nonadherent clot to a fairly solid mass that partially occludes the main vein. Within a few days the opposite leg may be affected by a typical phlebothrombosis involving the lower leg and thigh, clearly indicating operative interference. The question naturally arises, At what level should the vein be severed? Shall one perform a routine bilateral femoral division and attempt suctioning out the thrombi from the proximal portions of the veins, with the possible danger of leaving in some clot or dislodging it in the process of suctioning? Shall one divide the external or common iliac vein on one side and the common femoral vein on the other? The simplest solution to the problem appears to be to interrupt the inferior vena cava. The following case illustrates this point quite clearly.

CASE 1. M. S., a 34-year-old, married woman, had a pelvic operation performed on June 6, 1944. A moderate-sized cyst was removed from the right ovary and numerous

\*Presented at the annual meeting of the New England Surgical Society, Boston, September 20, 1944.

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adhesions were freed. The patient was discharged 2 weeks after an uneventful postoperative course. Ten days later she experienced moderate pain and swelling in the left leg and thigh. She was returned to the hospital, where shortly after admission she suffered a major pulmonary embolism. This was characterized by sharp substernal pain, cyanosis, a rapid, thready pulse, expectoration of bloody sputum and fear of impending death. Examination of both lower extremities revealed signs of deep venous thrombosis, the left more advanced than the right, extending to the groins. A diagnosis of bilateral, nonobstructive venous thrombosis, probably reaching into the iliac vessels, was made.

Under ether anesthesia, the inferior vena cava was exposed through a right lumbar incision. Two heavy braided-silk ligatures were applied to the lower vena cava, care being taken to avoid the lumbar veins. No attempt was made to search for intravenous clot. The patient's condition remained poor for 48 hours, but she gradually improved and was discharged from the hospital within 10 days. When last seen 2 months after the operation, she appeared to have undergone no ill effects from interruption of the vena cava. She experienced moderate discomfort in both legs after long periods of standing. Walking did not disturb her, and she carried on her usual household duties. Objectively there was no swelling in either leg.

In the second group of cases that may call for a ligation of the inferior vena cava, the indications are not quite so well defined, particularly since the source of the embolus may be entirely unknown and no clinical evidence of thrombosis may be available. Pathological and clinical observations preponderantly favor the role played by deep venous thrombosis of the lower leg in the production of pulmonary embolism. This phlebothrombosis may be very quiet and yet lethal in its manifestations, exhibiting no evidence of its presence until death ensues. Or the first intimation that such thrombosis exists may be the familiar signs of a pulmonary infarction, — evidence sufficient perhaps to justify division of the femoral vein. But if emboli continue to recur after such an operative procedure, is it correct to assume that thrombosis in the lower leg has been the instigating factor, even though there is no subsequent clinical manifestation of thrombosis? How perplexing this problem may be is shown by the following case.

CASE 2. M. O'B., a 52-year-old unmarried woman, had three minor pulmonary episodes, diagnosed as pulmonary infarctions, during a 4-week interval following the performance of a cholecystectomy. Search for a focus of thrombosis in the lower extremities was nonrevealing. A phlebogram was negative for obstruction in the deep veins of the leg. Despite all negative findings, bilateral division of the common femoral veins was done. No intravenous thrombus was discovered, and free bleeding was observed from the distal and proximal vein segments on both sides.

Two days following the operation, the patient presented a classic picture of sudden pulmonary embolism, with chest pain, marked dyspnea and cyanosis and expectoration of bloody sputum. Supportive treatment was instituted and the patient recovered. A subsequent electrocardiogram was negative. Within the following 12 days, two similar attacks, both almost lethal, occurred. Interruption of the inferior vena cava was contemplated, but the patient's condition interdicted any operative interference. She slowly responded to conservative measures and left the hospital within 4 weeks of the last attack. At no time during the hospital stay or since discharge has any clinical evidence of venous thrombosis been present in either leg.

Furthermore, there have been other cases in which repeated attacks of pulmonary embolism have occurred and no treatment except rest and seda-

tion was instituted, yet at no time during or after these attacks has any evidence of deep thrombosis in the lower limbs been present, even though the most painstaking search, including phlebography, was carried out.

One may thus postulate a propagating thrombus arising from some other source, such as the prostatic or uterine plexus, wending its sinister way through the hypogastric vein and the common iliac vein into the inferior vena cava. Anyone who is familiar with surgery of the female pelvis is aware of the tremendous size that the veins of the uterine plexus may attain. Their engorgement during pregnancy, in the presence of pelvic disease or in the course of routine postoperative convalescence, with its attendant immobilization, creates a most favorable medium for the formation and propagation of a silent thrombus. Likewise, in the male, the prostatic plexus gives a similar picture. This plexus of veins, sometimes termed the "prostaticovesical plexus," surrounds the prostate gland and the neck of the bladder. It receives the deep dorsal vein of the penis and veins from the seminal vesicles and empties into the hypogastric vein. All these veins may enlarge to considerable dimensions and become varicose and thrombosed. Hence, when the

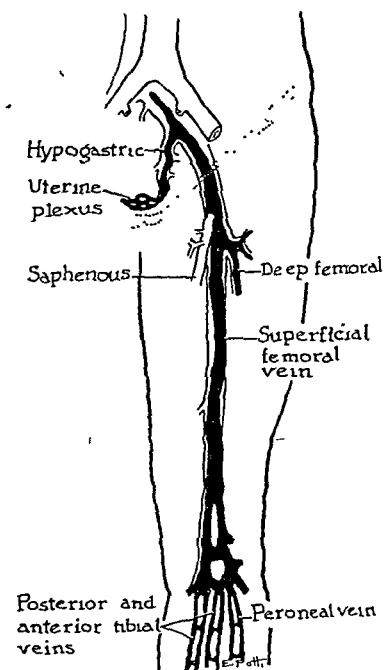


FIGURE 1. Sketch Showing Origin and Cause of Deep Venous Propagating Thromboses.

The thrombus may be initiated in the lower leg veins, or in the deep femoral system, or in the deep pelvic veins, such as the uterine or prostatic venous plexuses.

presence of so-called "silent thrombosis" is suspected the thrombotic process may well exist in one or several groups of deep veins, namely, the venous channels of the lower leg, the deep femoral veins and the venous plexuses of the pelvis (Fig. 1). When

the source of the embolus is unknown, the best guarantee of safety appears to be interruption of the inferior vena cava, such as was performed in the following case.

CASE 3. L. D. O., a 65-year-old, married woman, had a cholecystectomy performed on June 13, 1944, at which time an acute gangrenous gall bladder was removed. The convalescence was essentially uneventful and afebrile until the 19th postoperative day. During the next 4 days the pulse, temperature and respirations were elevated, and signs of pulmonary infarction were found in the right chest. X-ray studies confirmed this diagnosis. A repeat chest plate taken several days later showed a much larger area of infarction than at the first observation. The clinical course and x-ray findings suggested repeated pulmonary embolisms. There was no evidence of thrombosis in either lower extremity. Because of this negative finding, interruption of the inferior vena cava was performed under Pentothal-cyclopropane anesthesia through a right lumbar incision. The postoperative course was excellent, save for one or two gastrointestinal upsets. Except for a sense of heaviness and minimal swelling in both legs when standing, the patient has no complaints.

In the above case, an equally good result might have been obtained by bilateral division of the common femoral vein, but previous experiences in which repeated embolisms have occurred after such a procedure, with the belief that a silent propagating thrombosis might exist in the pelvic vessels, influenced me in ligating the inferior vena cava.

Several considerations present themselves in a discussion of ligation of the inferior vena cava. They include the pattern of the collateral circulation that follows on such an interruption, and the operative procedure and the state of the venous return from the legs after occlusion of the vena cava.

In a recent communication, Homans<sup>1</sup> has demonstrated the more satisfactory collateral circulation available when the common iliac vein, rather than the common femoral vein, is divided. A further significant clinical observation is made by the same writer, to the effect that there is much less venous congestion and swelling of the extremities following such a division. It should be pointed out that a parallel situation exists when the inferior vena cava is occluded. There is equally as rich a collateral venous pattern set up after such interruption as after division of the common iliac vein. The theoretical disadvantage of the former procedure, in relation to return blood flow from the legs, is the interference with shifting of blood from one side of the pelvis to the other — a situation that does not obtain when only one common iliac vein is obstructed. This apparent disadvantage, however, is not borne out by any serious clinical aftereffects with which I am familiar.

The collateral pathways available after ligation of the lower vena cava fall roughly into three groups — the superficial, the deep, and those of the ascending lumbar trunks. The first of them comprise the superficial circumflex iliac and the superficial epigastric veins, which connect the saphenous system with the superficial thoracic vein and those of the upper abdominal wall. The deep pathways are formed by the anastomosis of the deep circum-

flex iliac, superior epigastric and lumbar veins, thereby connecting the external iliac veins with the internal mammary and ascending lumbar veins. The ascending lumbar trunks begin in the pelvis on either side of the promontory of the sacrum and communicate with the sacral, common iliac, hypogastric and iliolumbar veins. As they ascend they connect with the lumbar veins, the inferior vena cava and the right renal vein. The right lumbar trunk becomes the azygos vein and terminates in the superior vena cava; the left continues as the hemiazygos vein and eventually enters the right azygos vein. Figures 2, 3 and 4 — the first two taken from

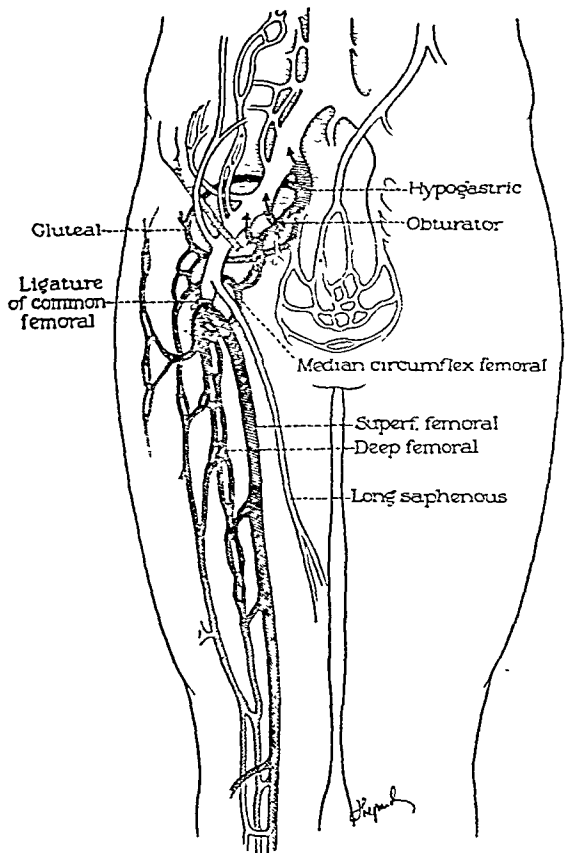


FIGURE 2. Diagrammatic Representation of the Venous Return and Collateral Blood Supply following Division of the Common Femoral Vein. (Reproduced from Homans<sup>1</sup> with permission of the publisher.)

the description by Homans — portray the essential differences in the collateral channels at various levels of interruption of deep veins.

Technically, the exposure and ligation of the lower vena cava is not so hazardous or so difficult as would first appear. Heretofore, the majority of ligations have been carried out as emergency procedures following operative accidents, particularly after nephrectomy. For obvious reasons, approach to the vena cava under such conditions is extremely formidable. Such a problem, of course, does not exist in an elective operation. Interruptions of the vena

cava have also been performed because of septic thrombosis in the deep pelvic veins.<sup>2</sup> The approach in these cases is always transperitoneal, because of the necessity of ligating the ovarian veins as well as

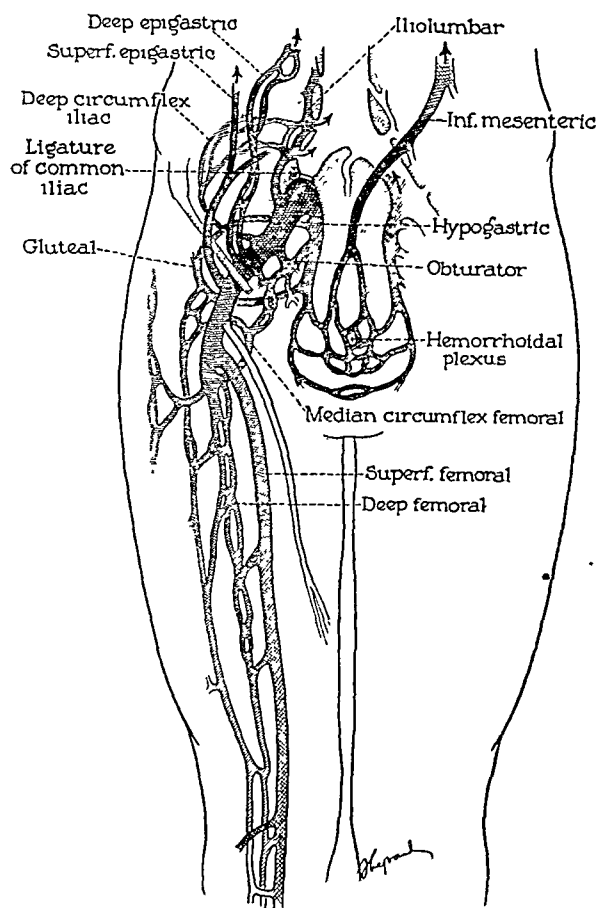


FIGURE 3. Diagrammatic Representation of the Rich Collateral Venous Circulation after Interruption of the Common Iliac Vein. (Reproduced from Homans<sup>1</sup> with permission of the publisher.)

the inferior vena cava. The left ovarian vein enters the left renal vein; the right ovarian vein flows directly into the inferior vena cava. In the presence of pelvic infection and septic thrombosis, possible dissemination of septic emboli by way of the blood stream into the kidneys and lungs demands the division of these vessels. In aseptic thrombosis or phlebothrombosis, this indication does not obtain. The ovarian veins are small, and very likely do not dilate enough to harbor a propagating thrombus of sufficient size to produce a major embolism. The approach to the inferior vena cava may therefore be entirely extraperitoneal.

One of two incisions may be employed. The first (Fig. 5) is that customarily used in exposing the right iliac vessels, and is made approximately parallel to the inguinal ligament extending laterally toward the flank. After retraction of the peritoneum mesially, the right common iliac vein is clearly brought into view; further retraction up-

ward and inward discloses the lower inferior vena cava. The alternate incision (Fig. 6) is placed higher up in the flank. It is the approach usually employed in the operation of lumbar sympathectomy. It gives ready access to the vena cava, and appears to be the preferable route. If troublesome bleeding is encountered, the better exposure rendered by the lumbar incision makes control of such a complication less difficult. Also, little manipulation is required in tying off the vena cava through this incision, a consideration if much thrombus is present in the iliac vessels. Actual ligation of the vena cava is done with two heavy braided-silk ligatures placed about the vessel 2 or 3 cm. apart. Caution should be used when placing these ligatures in the region of the lumbar veins. These veins, four in number, on either side of the lower vena cava may easily be injured in the maneuver of sliding the ties under the main venous trunk. It is necessary neither to open nor to divide the inferior vena

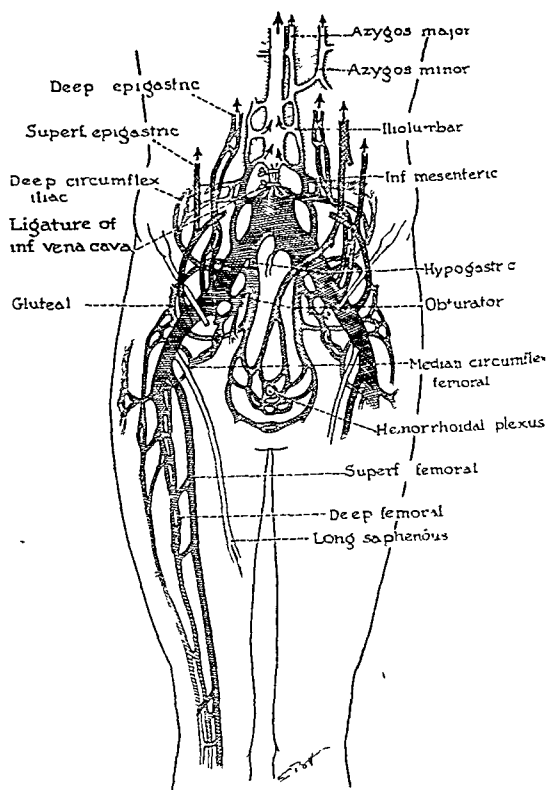


FIGURE 4. Diagrammatic Sketch Illustrating the Abundant Collateral Venous Supply following Ligation of the Inferior Vena Cava.

The venous return is comparable to that obtained when a bilateral common-iliac-vein interruption is performed.

cava. If a thrombus is contained within the vessel, not enough will be detached to be dangerous. Ligation will serve the purposes of interruption equally as well as division.

The determination of venous pressures in measuring the status of venous return

ing ligation of the inferior vena cava, is probably of considerable value. It is apparent that venous pressure is considerably raised following occlusion of a

rapidly after interruption of the vena cava. Theoretically, in cases of advanced age with failing myocardium, caution should be used in ligating the in-

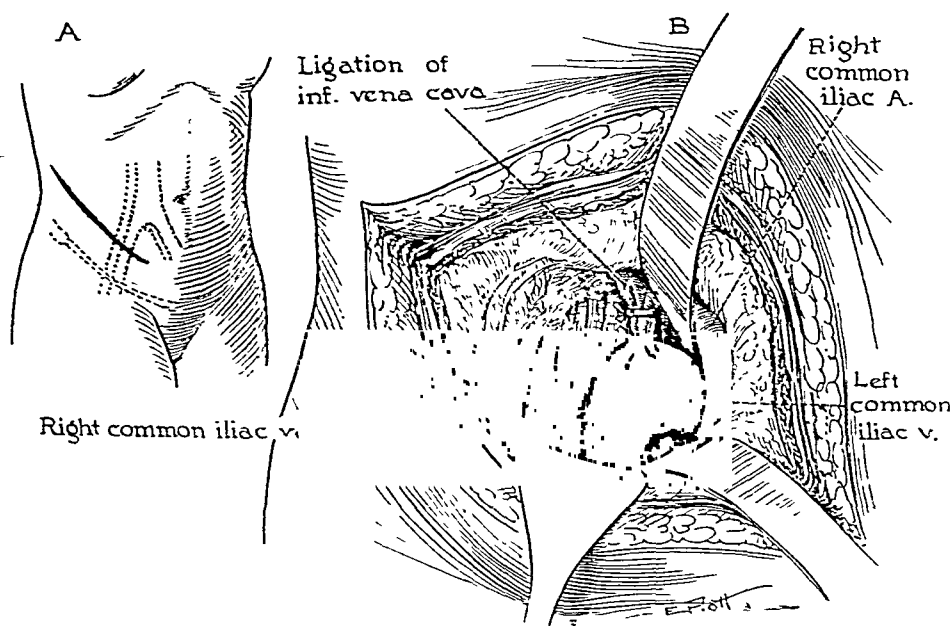


FIGURE 5. *The Abdominal Extraperitoneal Operative Approach to the Lower Inferior Vena Cava.*

main venous trunk, without, however, causing any undue effect on a normal heart muscle. If pressure in the great veins becomes excessive, the heart muscle responds by contracting more vigorously,

inferior vena cava. Further studies are necessary for fuller understanding of this problem.

Clinically, both the immediate and the remote effects of caval ligation are satisfactory. Eight cases

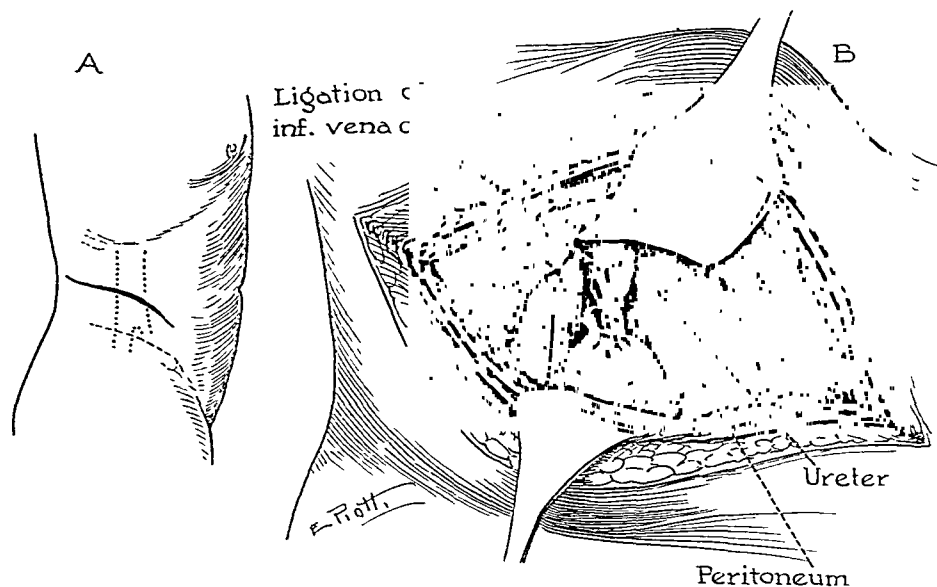


FIGURE 6. *The Lateral Extraperitoneal Operative Approach to the Inferior Vena Cava.*  
*The incision is the one customarily used in lumbar sympathectomy.*

propelling more blood into the arterial tree and thereby lowering venous pressure and maintaining it at a normal level. It is thus evident that venous pressure should return to normal quite

of interruption of the inferior vena cava have been performed in this series. In 5 of these, there had been obvious thrombotic involvement of the lower extremities; in 3, pulmonary embolism had oc-

curred but no source was evident. In no case have there been any untoward postoperative effects. Minimal discomforts, such as heaviness, numbness and moderate swelling, have been observed by patients, but are not of sufficient magnitude to interfere with their usual everyday duties. Edema of the legs, which at first thought seems to be of outstanding importance, is not so frequent or so pronounced as after division of the femoral vein, and with the passage of time usually clears up.

CASE 4. J. McC, a 41-year-old man, was brought to the hospital in December, 1939, following an unusual accident 8 weeks previously. He had been struck in the backs of both knees by an automobile bumper, suffering extensive contusions and abrasions but no fractures. Considerable swelling, coldness, numbness and mottled discoloration of both lower legs followed. On examination the pedal, popliteal and femoral pulsations were absent in both legs, which were markedly swollen and still showed signs of hematomas in both popliteal spaces. The feet were cold and cyanotic, but the patient could move his toes and feet without difficulty.

A transperitoneal exploration of the pelvic vessels was performed. Extensive thrombosis was observed in both right and left common iliac arteries and veins, leading up to the bifurcation of the aorta and vena cava. A left common iliac arterectomy, with removal of a 5-cm. segment of the vessel, was done. It was decided to tie off each common iliac vein, but profuse bleeding from one of the lower lumbar veins dictated an interruption of the inferior vena cava above the bleeding point. The patient recovered after a stormy and protracted convalescence. The immediate effect on the swelling of the legs was striking. Within 48 hours the edema began to subside and did not reappear even on standing. The legs have remained free of swelling since the operation (Fig. 7).

This case illustrates the rapid collateral anastomoses that are effected after interruption of the inferior vena cava, even in the presence of a fairly well-advanced venous thrombosis.

#### SUMMARY AND CONCLUSIONS

Two indications for interruption of the inferior vena cava have been suggested: when concurrent phlebothrombosis exists in both lower extremities and has extended to or above the inguinal ligament; and when pulmonary embolism has occurred and its source is not evident.

In one's enthusiasm for diagnosing lower-leg thromboses as the *bête noir* in pulmonary embolism, the fact that aseptic thrombosis may exist in the large pelvic vessels and initiate a serious embolism

should not be overlooked. If one is to operate on cases of deep venous thrombosis on suspicion alone, the best assurance that can be given for the patient's

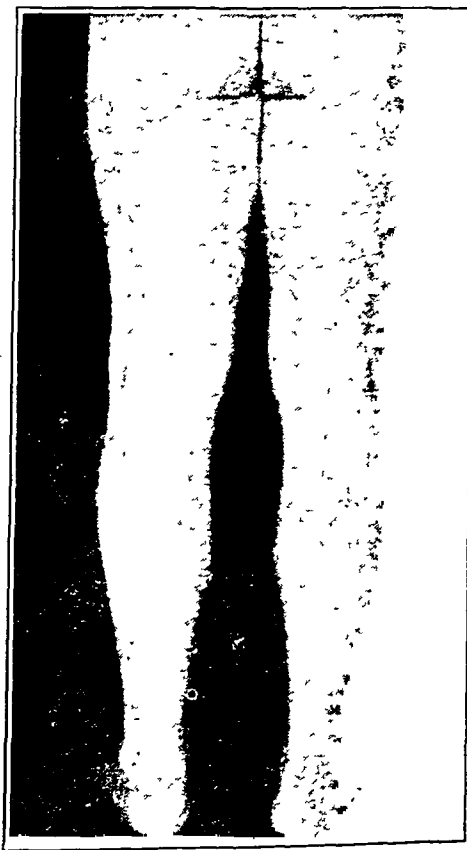


FIGURE 7. Photograph of the Patient's Legs (Case 4) Five Years after Ligation of the Inferior Vena Cava.

Note the absence of swelling. At no time following operation was any swelling apparent in either extremity.

safety is the highest possible ligation compatible with adequate venous return.

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## THE CRUVEILHIER-BAUMGARTEN SYNDROME\*

## Report of a Case

ALEXANDER BLAIN, III, M.D.,† AND MUIR CLAPPER, M.D.‡

DETROIT

INFREQUENTLY a venous hum or bruit occurs in the dilated collateral venous channels that may develop in portal obstruction. In 1942, Armstrong et al.<sup>1</sup> reviewed the 53 published cases of this phenomenon and added 2 cases of their own. Actually, 5 of the cases — including 1 of Armstrong's — showed persistence of a patent umbilical vein without portal obstruction. Since the review of Armstrong, several additional cases of portal obstruction associated with a venous hum heard over the dilated collateral veins have been reported, mainly by English and French authors.

## HISTORICAL CONSIDERATIONS

Pégot<sup>2,3</sup> in 1833 observed a patient who had dilated veins in the abdominal wall, a caput medusae and a loud venous hum at the umbilicus. Post-mortem examination revealed a widely patent umbilical vein associated with a small liver and spleen that were grossly normal in appearance. This case was again reported in 1835 by Cruveilhier,<sup>4</sup> who postulated that the patient had a congenital defect of the umbilical circulation with atrophy that was probably secondary to this defect. Baumgarten<sup>5</sup> in 1907 reported the case of a sixteen-year-old boy who had distended abdominal veins, ascites, splenomegaly, anemia and leukopenia. Post-mortem examination revealed a widely patent umbilical vein, splenomegaly "not of the Banti type" and an atrophic liver, with subcapsular increase in interlobular connective tissue. It was Baumgarten's belief that the disease was due to congenital failure of obliteration of the umbilical vein with hypoplasia of the liver. He emphasized the absence of a well-developed cirrhosis. Sappey,<sup>6</sup> however, in 1859 stated that the large vein found in the falciform ligament in some cases was independent of the umbilical vein.

Thayer's<sup>7</sup> review of the 19 cases published up to 1911 demonstrated that a majority of the cases that presented a venous hum had good evidence of cirrhosis of the liver without a patent umbilical vein. Thayer added a case from the Johns Hopkins Hospital in which the venous hum was definitely associated with a dilated collateral circulation due to portal obstruction in a patient with hepatic cirrhosis.

Hanganutz<sup>8</sup> in 1922 collected 6 cases of partial or total persistence of the umbilical vein in what he

termed "Cruveilhier-Baumgarten cirrhosis." Several authors subsequently published case reports under this title. Later Fiessinger and Michaux<sup>9</sup> analyzed the reported cases together with their own cases and concluded that Cruveilhier-Baumgarten cirrhosis was not truly a disease entity.

Armstrong et al.<sup>1</sup> accepted the term "Cruveilhier-Baumgarten syndrome" as applying to those cases having a clinical picture of portal obstruction featured by a loud abdominal murmur and thrill and periumbilical venous distention. After analyzing the data of the published cases, they accepted only 4 as having the true congenital abnormality that results in Cruveilhier-Baumgarten disease as originally described. They were able to add 1 case of their own from the Los Angeles County Hospital.

In differentiating the true Cruveilhier-Baumgarten disease, a very rare congenital anomaly of which only 5 well-proved examples are known, and the Cruveilhier-Baumgarten syndrome, which is usually the result of cirrhosis of the liver, Armstrong states:

... any patient having portal hypertension, generally with splenomegaly, and in whom evidence in the form of visible veins, murmurs and thrill of excessively prominent umbilical circulation exists, merits the diagnosis of *Cruveilhier-Baumgarten syndrome*. . . . Those cases which show at necropsy patency of the umbilical vein itself together with atrophy and little or no fibrosis of the liver would then be considered as examples of *Cruveilhier-Baumgarten disease*.

Lutembacher<sup>10</sup> in 1936 reviewed the subject of the genesis of the venous hums and proved that they arise from veins, being most intense at the point where a small vein enters a dilated vein. The bruits have most often been heard either in the epigastrium over the course of the falciform ligament (containing dilated periumbilical veins) or over dilated superficial veins. They have also been heard in the splenic area, over dilated coronary veins and over the liver. The murmurs heard in the Cruveilhier-Baumgarten syndrome have been described as "the roaring of a wind through a cave or humming of a top" (Gambarati, quoted by Thayer<sup>7</sup>) and, in 1 case (Catti<sup>11</sup>), as "a musical ringing sound like that of an Aeolian harp."

The murmur in the following case was continuous in nature and sounded somewhat like a hurricane. It was best heard over a prominent superficial varicosity near the umbilicus.

## CASE REPORT

A. M., a 46-year-old man of Rumanian birth, was admitted to the Detroit Receiving Hospital on March 23, 1944, complaining of swollen legs and a distended abdomen of 8 months'

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duration. The past history revealed chronic alcoholism of long standing. He had been imbibing three or four bottles of beer and several drinks of whisky daily since the age of 14. It is of unusual interest that the abdomen had been tapped for ascites 23 years previous to the present illness after a progressive enlargement of 3 months' duration. Four thousand cubic centimeters of fluid was removed. Following the paracentesis there was no abdominal distention until the onset of the present illness. In July, 1943, the patient noticed a slight swelling near the umbilicus, just under the skin and easily reducible with a finger. This mass was "blue" (apparently a vein) and marked the onset of a gradual and generalized enlargement of the abdomen that progressed until the time of admission. The abdominal swelling was painless until 1 month prior to admission. Edema of the ankles had been present for 5 months. There was no cough, dyspnea, palpitation, hematemesis, tarry or bloody stools or the like. A thorough dietary history revealed no specific nutritional deficiency but rather a generally poor food intake.

Physical examination revealed a well-developed, slightly icteric man with a markedly distended abdomen and pitting edema of the ankles. Over the tense abdominal surface were many large dilated veins that filled from below upward. These veins fused about the umbilicus to form a classic caput medusae (Fig. 1). Numerous spider angiomas were present over the shoulders, back and abdomen. The tongue was smooth and of a striking magenta color. The head and neck were otherwise normal. Examination of the chest revealed a few moist crackling rales at the lung bases. The heart was slightly enlarged to the left, and there was a soft blowing systolic murmur at the apex. Abdominal examination revealed shifting dullness and a fluid wave. A continuous thrill was easily palpated over the large dilated vein just above and to the right of the umbilicus (Fig. 2). Auscultation in this area revealed a continuous murmur that was extremely loud but varied in intensity ("like a hurricane"). Pressure on the vein below this dilatation obliterated the venous hum and thrill. The scrotum and the lower extremities from the hips down exhibited marked pitting edema.



FIGURE 1. Infrared Photograph Showing the Caput Medusae.

The liver and spleen could not be palpated. The rectal and neurologic examinations revealed nothing significant.

The serum albumin level was persistently low, varying from 1.6 to 2.6 gm. per 100 cc. in six determinations. The lowest serum globulin level was 4.2 gm. per 100 cc., and the highest 4.7 gm. The amount of urobilinogen in the urine on repeated examination was markedly increased as measured by a rough dilution method, positive tests being obtained

on urine diluted as much as 1:400. After the oral administration of 6 gm. of sodium benzoate in the performance of the hippuric acid test, an amount of hippuric acid equivalent to 1 gm. of benzoic acid was excreted in a 4-hour urine specimen. Repeated icterus indices varied from 10 to 50 units



FIGURE 2. Photograph Showing the Varicosity near the Umbilicus over Which the Intensity of the Venous Hum Was Greatest.

The van den Bergh reaction was direct, immediate and positive. The serum bilirubin was 0.9 mg. per 100 cc. Hematologic studies revealed a hemoglobin of 11 gm. per 100 cc. and a red-cell count of 3,810,000. This gave a color index of 1.01. The white-cell count was 9950, with 82 per cent neutrophils (68 per cent filamented), 9 per cent lymphocytes, 7 per cent eosinophils and 2 per cent monocytes. The neutrophils contained toxic granulations. The platelet count was 297,000. The bleeding time was 2.5 minutes, the coagulation time 2.5 minutes, and the prothrombin 78 per cent of normal. Clot retraction began in 45 minutes and was complete in 4 hours. Urinalyses were persistently negative. Repeated stool examinations were benzidine-positive and contained bile. Over 1000 cc. of ascitic fluid was aspirated in each of three paracenteses. This fluid was negative for neoplastic cells, blood and tubercle bacilli. Its specific gravity of 1.016, and an albumin content of 8.4 gm. per 1000 cc. showed it to be a transudate.

An electrocardiogram revealed a sinus tachycardia and evidence of myocardial damage—early left ventricular in type. A stethogram recording made simultaneously with the electrocardiographic tracing showed a continuous murmur the intensity of which was greatest at the umbilicus. A chest x-ray film showed elevation of both leaves of the diaphragm due to the abdominal distention by fluid. Above the diaphragm there were patchy areas of atelectasis at both lung bases. The venous pressure in the right antecubital vein was equivalent to that of 6 cm. of saline solution, as contrasted with a venous pressure of 17 cm. in a dilated superficial vein near the site of origin of the venous hum.

On April 18, the patient suddenly became drowsy and lapsed into coma. He vomited and developed Kussmaul breathing, and died on the following day.

Unfortunately, permission for autopsy could not be obtained.

This patient's long history of chronic alcoholism, together with the hypoproteinemia, icterus, abnormal benzoic acid excretion, urinary urobilinogen and the findings of portal obstruction, established the diagnosis of cirrhosis of the liver. The demon-

stration of a venous hum in association with proved cirrhosis of the liver suggests strongly that this case is an example of the Cruveilhier-Baumgarten syndrome rather than Cruveilhier-Baumgarten disease, in which the venous hum is due to a persistence of a patent umbilical vein. In the absence of post-mortem examination we cannot be absolutely certain that a patent umbilical vein was not also present, but the rarity of this anomaly makes this possibility quite unlikely.

SUMMARY

A case of hepatic cirrhosis presenting the features of the Cruveilhier-Baumgarten syndrome is reported. A brief history of this syndrome and its relation to the extremely rare congenital Cruveilhier-Baumgarten disease are discussed.

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MEDICAL PROGRESS

ECZEMA\*

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**A** DIAGNOSIS of "eczema" is never a sufficient one. In recent years the term has come to be used more and more for those cases in which there is a suggestion that the cause of the dermatitis is allergy, and that the eczema depends on a sensitiveness to one or another foreign substance that affects the patient either by ingestion, by inhalation or by direct contact.

The present conception of eczema is remarkably new. In 1892, Besnier<sup>1</sup> wrote a "*Première note et observations préliminaires pour servir d'introduction à l'étude des prurigos diathésiques*." He recognized that certain dermatoses that came and went in attacks depended on something wrong with the body as a whole and were not merely a disturbance that was limited to the skin itself. It was twenty-two years later, in 1914, that Rasch,<sup>2</sup> a Norwegian, named eczema of a certain variety "prurigo of Besnier." The description referred to the type of eczema which occurs in older children and young adults, and in which the distribution of lesions to the face, neck and antecubital and popliteal spaces is particularly characteristic. Brocq called it "neurodermite," as Hill<sup>3</sup> has explained, but in more recent years it has passed under the name of "flexural eczema" and sometimes of "eczema with lichenification." Nowadays it is best designated as "atopic" dermatitis or perhaps "allergic dermatitis" or "atopic eczema," the adjective "atopic," proposed

by Coca,<sup>4</sup> referring to the factor of inheritance, as well as to a mechanism comparable to that of hay fever and asthma.

Meantime, Schloss's<sup>5</sup> study of the baby sensitive to eggs, almonds and oatmeal was published in 1912. Goodale<sup>6</sup> described horse asthma in 1914, and in 1916 came the first comprehensive paper on human sensitization — that by Cooke and Vander Veer.<sup>7</sup> Also in 1916, Blackfan<sup>8</sup> tested eczematous infants with various substances and demonstrated that a high proportion of them were skin-sensitive to egg white. This paper furnished the first real evidence that allergy may be a factor in infantile eczema. The comprehensive studies of Walker<sup>9</sup> on asthma began in 1917. In 1920, Ramirez<sup>10</sup> likewise made skin tests on infants with eczema and showed that 30 of 78 cases were skin-test-positive. At the same time he pointed out that those children who suffered also from asthma and hay fever were likelier than others to show positive skin reactions.

Treatment on the basis of eliminating certain foods, especially eggs and cow's milk, from the diet began. In 1923, O'Keefe<sup>11</sup> found that the diet treatment was successful even though he was unable to demonstrate positive skin tests, and he first pointed out that "variations in the threshold of sensitivity in various tissues may be the factor which determines whether hay fever, asthma or eczema will result from foreign proteins with which the tissues are brought in contact."

In the meantime, another type of eczema was in process of description when Bloch<sup>12</sup> found that

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duration. The past history revealed chronic alcoholism of long standing. He had been imbibing three or four bottles of beer and several drinks of whisky daily since the age of 14. It is of unusual interest that the abdomen had been tapped for ascites 23 years previous to the present illness after a progressive enlargement of 3 months' duration. Four thousand cubic centimeters of fluid was removed. Following the paracentesis there was no abdominal distention until the onset of the present illness. In July, 1943, the patient noticed a slight swelling near the umbilicus, just under the skin and easily reducible with a finger. This mass was "blue" (apparently a vein) and marked the onset of a gradual and generalized enlargement of the abdomen that progressed until the time of admission. The abdominal swelling was painless until 1 month prior to admission. Edema of the ankles had been present for 5 months. There was no cough, dyspnea, palpitation, hematemesis, tarry or bloody stools or the like. A thorough dietary history revealed no specific nutritional deficiency but rather a generally poor food intake.

Physical examination revealed a well-developed, slightly icteric man with a markedly distended abdomen and pitting edema of the ankles. Over the tense abdominal surface were many large dilated veins that filled from below upward. These veins fused about the umbilicus to form a classic caput medusae (Fig. 1). Numerous spider angiomas were present over the shoulders, back and abdomen. The tongue was smooth and of a striking magenta color. The head and neck were otherwise normal. Examination of the chest revealed a few moist crackling rales at the lung bases. The heart was slightly enlarged to the left, and there was a soft blowing systolic murmur at the apex. Abdominal examination revealed shifting dullness and a fluid wave. A continuous thrill was easily palpated over the large dilated vein just above and to the right of the umbilicus (Fig. 2). Auscultation in this area revealed a continuous murmur that was extremely loud but varied in intensity ("like a hurricane"). Pressure on the vein below this dilatation obliterated the venous hum and thrill. The scrotum and the lower extremities from the hips down exhibited marked pitting edema.



FIGURE 1. Infrared Photograph Showing the Caput Medusae

The liver and spleen could not be palpated. The rectal and neurologic examinations revealed nothing significant.

The serum albumin level was persistently low, varying from 1.6 to 2.6 gm. per 100 cc. in six determinations. The lowest serum globulin level was 4.2 gm. per 100 cc., and the highest 4.7 gm. The amount of urobilinogen in the urine on repeated examination was markedly increased as measured by a rough dilution method, positive tests being obtained

on urine diluted as much as 1:400. After the oral administration of 6 gm. of sodium benzoate in the performance of the hippuric acid test, an amount of hippuric acid equivalent to 1 gm. of benzoic acid was excreted in a 4-hour urine specimen. Repeated icterus indices varied from 10 to 50 units



FIGURE 2. Photograph Showing the Varicosity near the Umbilicus over Which the Intensity of the Venous Hum Was Greatest.

The van den Bergh reaction was direct, immediate and positive. The serum bilirubin was 0.9 mg. per 100 cc. Hematologic studies revealed a hemoglobin of 11 gm. per 100 cc. and a red-cell count of 3,810,000. This gave a color index of 1.01. The white-cell count was 9950, with 82 per cent neutrophils (68 per cent filamented), 9 per cent lymphocytes, 7 per cent eosinophils and 2 per cent monocytes. The neutrophils contained toxic granulations. The platelet count was 297,000. The bleeding time was 2.5 minutes, the coagulation time 2.5 minutes, and the prothrombin 78 per cent of normal. Clot retraction began in 45 minutes and was complete in 4 hours.

Urinalyses were persistently negative. Repeated stool examinations were benzidine-positive and contained bile. Over 1000 cc. of ascitic fluid was aspirated in each of three paracenteses. This fluid was negative for neoplastic cells, blood and tubercle bacilli. Its specific gravity of 1.016, and an albumin content of 8.4 gm. per 1000 cc. showed it to be a transudate.

An electrocardiogram revealed a sinus tachycardia and evidence of myocardial damage—early left ventricular in type. A stethogram recording made simultaneously with the electrocardiographic tracing showed a continuous murmur the intensity of which was greatest at the umbilicus. A chest x-ray film showed elevation of both leaves of the diaphragm due to the abdominal distention by fluid. Above the diaphragm there were patchy areas of atelectasis at both lung bases. The venous pressure in the right antecubital vein was equivalent to that of 6 cm. of saline solution, as contrasted with a venous pressure of 17 cm. in a dilated superficial vein near the site of origin of the venous hum.

On April 18, the patient suddenly became drowsy and lapsed into coma. He vomited and developed Kussmaul breathing, and died on the following day.

Unfortunately, permission for autopsy could not be obtained.

This patient's long history of chronic alcoholism, together with the hypoproteinemia, icterus, abnormal benzoic acid excretion, urinary urobilinogen and the findings of portal obstruction, established the diagnosis of cirrhosis of the liver. The demon-

including the importance of skin tests. In the next year he with Pratt<sup>21</sup> showed that in those infants sensitive to cow's milk the lactalbumin caused more trouble than the casein. It is to be wondered whether cottage cheese might not be a useful addition to an otherwise restricted diet.

In the meantime, Hampton and Cooke<sup>22</sup> and later Simon<sup>23</sup> discovered that human dander contains an allergen to which certain human beings become sensitive and that in certain infants the eczema depends on an allergy to human dander. Hampton and Cooke found that skin reactions to human dander were positive in a few cases but not in enough to support the idea that this dander is a frequent cause of eczema. Simon, on the other hand, found that skin tests by the patch method applied to young children with eczema showed positive reactions to human dander in 15 of 20 cases, whereas in 23 non-eczematous children of the same age there was only a single positive reaction. In a few cases, the prompt improvement that followed the avoidance of contact with human dander was striking. Finally, Simon was able to show that the lesions could be reproduced when, for example, the mother rubbed her hair on the lower abdomen of her child. In another paper he<sup>24</sup> found that extracts made from the scales of patients with seborrheic dermatitis gave reactions quite like those of human dander, whereas the scales from patients with psoriasis or exfoliative dermatitis showed nothing. All this work was done by the patch method of testing, since the scratch test remained negative.

One may conclude that in infantile eczema the factor of allergy is present, and in certain cases the lesions disappear when contact with the food or possibly with the dust is removed. On the whole, however, it is recognized more and more that in these children there is some fundamental disturbance that remains unexplained.

Several papers suggest the new trend. Engman and MacCardle<sup>25</sup> found that albino rats when fed a diet deficient in magnesium developed lesions similar to those of neurodermatitis. The vitamins have been studied, as might be expected. Kunz<sup>26</sup> examined the riboflavin metabolism in 2 cases. Harris and Gay<sup>27</sup> treated 20 cases of infantile eczema with large doses of vitamin B complex. In 2 of them there was complete healing and in 11 there were various degrees of improvement, but in 7 cases there was no change. The absorption of vitamin A was found by di Sant'Agnese and Larkin<sup>28</sup> to be impaired in 4 cases, but each patient was in extremely poor general condition, besides having severe eczema. On the other hand, Frei<sup>29</sup> varied the amount of vitamin A (carotene) in the diet of guinea pigs and studied the ability to sensitize them to old arsphenamine. No significant influence could be demonstrated.

More promising, perhaps, is a new suggestion about fat in eczema. Burr<sup>30</sup> showed pictures of a

child before and after treatment with two or three teaspoonfuls of lard each day for a month. The eczema cleared entirely, and the author explains that fat has a sparing action on vitamin B<sub>6</sub>, that linoleic acid is important to the health of the skin, and that rats fed on a fat-free diet develop scaly skin with retarded growth, and later kidney lesions. This paper is reminiscent of older theories that eczema depends on too much fat in the diet.

#### ATOPIC DERMATITIS IN YOUNG ADULTS

In the Army and Navy, eczema is always troublesome, although fortunately the number of cases is not great. In 1943, French<sup>31</sup> reporting on allergy clinics in the Fourth Service Command, included 1100 cases of eczema as against 8500 cases of asthma and 5300 cases of hay fever. In the Navy, on the other hand, allergic skin diseases, according to Sulzberger,<sup>32</sup> comprised 8875 cases, whereas asthma and hay fever together numbered only 1257 cases. There were altogether 33,539 cases of skin diseases in the area described. Hampton and Rand<sup>33</sup> studied those men who were examined for certificates of disability for discharge on account of diseases of allergy. Of 1633 subjects, 286 had asthma, and 86 of them were discharged; 448 had hay fever, and 1 was discharged; 117 had urticaria, and 7 were discharged; 24 had atopic eczema, and 2 were discharged; and 35 had contact dermatitis, and 1 was discharged. Gold and Bazemore,<sup>34</sup> of Camp Blanding, give the clinic admission rate for asthma as 9.5 per 1000, for hay fever 3.3 and for eczema 12.3. The considerable variation of these figures is interesting; in some areas asthma seems much more important than eczema, whereas in other places the conditions are reversed. Presumably, the discrepancies depend on the difficulty of accurate diagnosis or on the classification used.

In the atopic dermatitis of adults, hypersensitivity to foods plays a part in not over 10 or 15 per cent, according to Osborne, Jordon and Hallett.<sup>35</sup> In their paper, stress is laid on external contact and environmental allergy pointing to wool, silk, feathers, other epidermals, soaps and laundry chemicals. As they say, a visit to the home of the patient is indispensable. Stroud<sup>36</sup> has commented on this, writing, "Success in the treatment of allergic dermatitis is proportionate to knowledge of the causative factors." Hill<sup>37</sup> has shown that with increasing age the importance of environmental allergy (dust substances) rapidly increases. Scratch tests with dusts were positive in only 10 per cent of 38 eczematous infants, but after the age of one they became positive in 37 per cent and after two in 50 per cent. Feinberg<sup>38</sup> stresses the molds, describing 14 cases in which the eczema became much worse during the pollen and mold seasons. In a number of patients, I have found that the eczema cleared when the patient went away from home and recurred on his return. Such a history is always im-

when certain chemical substances like quinine, iodoform and turpentine were applied to the unbroken skin and were held in contact for some hours, areas of typical eczema developed on the test site. He came to the conclusion that the so-called "constitution of the skin" was the decisive factor in producing the reaction. Thus, when a patient with horse asthma was tested by this patch test with horse protein, an area of eczema developed in the arm, whereas when normal persons were tested in the same way, no reaction resulted. For some years it was not appreciated that the kind of eczema associated with asthma and hay fever and dependent on a factor of inheritance was quite different from the other kind of eczema that was localized to exposed surfaces and dependent on direct sensitization of a small area of exposed skin.

Recently, Cooke<sup>13</sup> has questioned the propriety of distinguishing so sharply between atopic eczema and contact dermatitis. Whereas it is quite true that both disorders depend on allergy, the facts, first that atopic eczema is often associated with other evidences of allergy whereas contact dermatitis is not, second that atopic eczema is not nearly so frequent as contact dermatitis, — the incidence of poison ivy, for example, is admittedly high, — and third that passive transfer antibodies (reagins) can be demonstrated in atopic eczema but not in contact dermatitis, make it reasonable to distinguish them.

#### CLASSIFICATIONS

Many authors have classified eczema. Several old names based on the clinical appearance — the morphology of the eczema — have been given up, and new names have been added. Seborrhea, with its oily skin and distribution to the hair line, the face and the upper portions of the chest and back, probably does depend on a disturbance of the skin itself.

Fungus disease, often hard to distinguish from eczema, is found oftener on the feet and hands, in the crotch, in the axillas and sometimes on the neck. In most cases it is possible to recognize the two types of eczema due to allergy. In atopic dermatitis, the characteristic feature is the typical distribution of the lesions to the face, neck and cubital and popliteal spaces. Skin tests made by the scratch or intradermal method show immediate positive reactions of the wheal and erythema type, and reagins that can transfer the skin sensitiveness to a local test site on the arm of a normal person are found in the blood. In contact dermatitis, the lesions are on exposed parts — usually the hands and face. Here the foreign substance reaches the skin by direct contact and not through the blood stream underneath. Whether this type depends also on heredity is not clear; the majority of people are sensitive to poison ivy, and in industry the frequency of dermatitis that involves the hands and

sometimes the face is greater than that of hay fever or asthma.

Atopic dermatitis can be divided for convenience into the infantile and adult types. In both, itching is the most significant feature. In infancy the lesions are on the face, where vesiculation and later oozing and crusting are characteristic. In older children and young adults vesiculation is not so marked, and in place of it comes lichenification, with thickening of the skin and later pigmentation. Although it is probably true that the two kinds of eczema differ chiefly in the location and concentration of sensitizing antibodies and so in the degree of clinical involvement, and that the differences may be greater in quantity than in kind, it is of practical importance to distinguish them, if only because in the one type the investigator looks for food or dust as the cause, whereas in the other he considers cosmetics, soaps and dyes, as well as chemicals in wide variety.

#### ATOPIC ECZEMA IN CHILDHOOD

Hill<sup>3</sup> has written, "To talk about eczema is easy; to cure the patient is quite another matter." In 1935 he<sup>14</sup> wrote an extremely interesting paper on the evolution of atopic dermatitis. He showed how the infantile form may subside of itself within a year or two when the child outgrows his sensitiveness, whereas in other cases this early type merges by slow degrees into the adult type, with thickening in place of weeping. Hill believes that the presence of a positive skin reaction to egg, which is observed in at least half the cases, is easy to explain. Egg is a protein easily digested by the adult; it is a common food, and it has been shown that egg can pass unchanged through the intestinal wall and the placenta so as to sensitize the fetus in utero. The significance of the positive skin test is not quite so easy to explain. In some cases there is great improvement when egg is withdrawn from the diet, but in most it is impossible to demonstrate any clinical relation between the elimination of egg and the improvement of the eczema: indeed, most of the infants have never had egg. Moreover, as Hill explains, it is not possible to produce atopic sensitization in a normal nonatopic person no matter how much egg white may have been given by injection. "Precipitins," he writes, "are produced but never eczema, asthma or hay fever. . . . The infant is prepared for eczema by his sensitivity to egg, but the actual eczema may be brought about by other causes of which nothing definitely is known." Smyth et al.<sup>15</sup> were able to produce striking relief in 47 of 160 cases by changes in diet based on the finding of positive skin reactions to foods.

After 1935 there was a hiatus in the study of infantile eczema. Sulzberger and his co-workers<sup>16-19</sup> did much to clarify the relations between this and other forms of skin disease. In 1940, Hill<sup>20</sup> presented a useful discussion of the diagnosis and treatment,

taneous hypersensitiveness to the drug, and he cautions against the indiscriminate use of sulfonamides in local treatment, which may sensitize the patient and so preclude the subsequent use of these drugs should serious illness supervene. Shaffer, Lentz and McGuire<sup>54</sup> have also found that sensitiveness to sulfathiazole can be induced by local therapy and subsequently elicited by oral medication.

As a test for sulfonamide hypersensitiveness, Leftwich<sup>55</sup> has made an important contribution. In tests for drug allergy, the application of most drugs by themselves to the skin produces no local reaction. The reaction must depend on a chemical combination between the drug and the serum protein. Leftwich found that the serum of patients who are saturated with the sulfonamide drugs and whose blood level is therefore high is an extremely useful testing agent. It is important that the donor patient shall have received the drug for at least five days and that the serum be used fairly soon after its separation. It is also important that the serum from a normal person be drawn at the same time and be kept under the same conditions so that the observations can be controlled. Leftwich reports that when the sulfonamide-bearing serum was injected intradermally into 30 patients who were clinically sensitive to the sulfonamide drugs, the results were positive in 28, with a wheal and erythema reaction that appeared in fifteen minutes. This may be significant particularly if the findings can be confirmed.

The legal aspects of contact dermatitis, especially in connection with industry and occupation, are sometimes complex. The employer has provided the specific substance, but the worker has provided the kind of tissue that is capable of developing a sensitiveness to that substance. Each of the two factors is necessary, and it is not always easy to separate them. Downing<sup>56</sup> has discussed the matter in an interesting paper.

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To repeat, the diagnosis of eczema is never a sufficient one. The problem is always complicated, but if one tries to visualize the probable mechanism that is operating in the particular patient, it is easier to find the cause through a better classification of the possible factors. As usual in the study and treatment of all the diseases due to allergy, it is the clinical history taken from the point of view of the detective more than from that of the physician that leads to the proper solution. In doing this, however, one must at least know what the possibilities are. In the background of all these cases there is a fundamental disturbance of normal physiology; this is a platitude that cannot be disregarded.

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portant and emphasizes once more the need for great care in history taking. It is always worth while to repeat the two most important points. First, one should record the passage of time and the relation to various foods and events by the actual dates on which they occurred and try to explain the end of the attack just as carefully as the onset. Secondly, one should account for all the time from the beginning of the disease to the present. If there was an interval of a year or two or perhaps of only a few months in the summer when the skin was quite clear, it is essential that this fact be noted in the history. Often such knowledge leads to the discovery that during the free period the patient was sleeping in a different house or perhaps living and sleeping in a different room in his own home.

Some years ago, Becker<sup>39</sup> laid stress on the fact that treatment of the patient as a whole was quite as important as treatment of his eczema. A woman who had had an eruption on the neck was playing thirty-six holes of golf every day and was in a state of chronic fatigue. With proper advice directed toward the improvement of general hygiene, the eczema cleared, even though contact with necklaces, dresses and a mink coat were the same after as before her visit to the physician.

The treatment of atopic eczema in adults is not easy; there is no specific treatment. Local treatment is necessary, but one should realize that the ointment or wash that does good in one case may be useless in the next. All too often one finds that too much local treatment does more harm than good. Potassium chloride, extra vitamins and nonspecific therapy of various kinds have all been used with success in certain cases but without effect in others. The ingestion of lard mentioned above for infantile eczema has been tried in older patients by Finnerud, Kesler and Wiese<sup>40</sup> with little evidence of success.

#### CONTACT DERMATITIS

In writing a review of the literature of drug allergy, I<sup>41</sup> was impressed by finding that in different patients the same drug might cause a variety of manifestations. Arsenic, for example, might cause in different cases a diffuse generalized dermatitis medicamentosa, asthma, agranulocytosis or a local contact dermatitis. This finding was an excellent demonstration that sensitiveness depends on the concentration of antibodies in certain tissues that are more sensitized than others. As described above, the principles of contact dermatitis are somewhat the same as those for atopic eczema, but they vary in degree; the sensitiveness is not general but is often confined to one area of the skin. The so-called "fixed drug eruptions" are particularly interesting, for in this condition the patient has a certain spot, perhaps on the thigh, face or arm, that always flares up when the drug is taken by mouth or by hypodermic needle. This is hardly a contact dermatitis,

but it illustrates the principle of localized tissue sensitiveness.

Contact dermatitis becomes increasingly important in industry as more and more complex chemical substances are devised. In contact dermatitis, the typical lesions are often on the hands; the backs of the fingers flare when the surgeon puts on the wrong kind of rubber gloves or the pharmacist or dentist comes in contact with novocain or quinine or other chemicals. They may be on the face, much trouble arising from cosmetics. Hazen<sup>42</sup> declares that the most frequent cause of dermatitis of the eyelids is nail polish. Howell<sup>43</sup> found that all brands of nail polish could cause the trouble, and Shelton<sup>44</sup> incriminated the nail-enamel foundation. Epstein<sup>45</sup> described the case of a mother and two daughters, aged four and six, who developed a contact dermatitis from hair lacquer pads. In the children the lesions at first suggested mumps because of the distribution and swelling, but later on, patch tests with the lacquer pads gave positive reactions. Pyle and Rattner<sup>46</sup> report the case of a medical officer who developed an inflammation of the eyelids and conjunctivas while preparing solutions of penicillin. Schwartz<sup>47</sup> has described 1904 cases constituting 30 per cent of those who worked in an explosive factory producing tetryl. The face, neck, eyes and all parts touched with the soiled hands are involved, and if exposure continues anemia and leukopenia may follow. Schwartz, Peck and Dunn<sup>48</sup> describe a dermatitis that depends on ureaformaldehyde and phenolformaldehyde resins, and Peck<sup>49</sup> finds that certain cutting oils and solvents that remove the fats and oils and dry the skin cause a local dermatitis. Baker's eczema is not frequent. At first it was thought that the trouble came from the ammonium persulfate and other substances added to the flour to make it easier to handle, but patch tests with these substances showed no reactions, and Van Vonno and Struycken<sup>50</sup> concluded that the trouble depended on the wheat flour itself.

The reactions that come from the sulfonamide drugs are of more practical interest. These are of great variety, ranging from a severe generalized exfoliative dermatitis in the case described by Johnson<sup>51</sup> to a local reaction when a drug is applied for local treatment. Kasselberg<sup>52</sup> described the case of a young man who had been treated with sulfathiazole for gonorrhea. Twenty days later the drug was changed to sulfamerazine, and after forty-eight hours a generalized macular eruption appeared, which three days later turned into a pemphigus-like disease, with numerous bullas and blebs filled with straw-colored fluid. One forgets that to produce sensitiveness, either local or general, one must follow the principles of the classic anaphylaxis experiment with its three factors — first the sensitizing dose, second a time interval and third the test or shocking dose. Park<sup>53</sup> has described 12 cases in which local sulfonamide therapy resulted in a cu-

became gradually elevated to 20,000, with 75 per cent monocytes, 9 per cent lymphocytes and 16 per cent monocytes; toxic granules were prominent. Despite repeated transfusions the red-cell count could not be maintained above 3,000,000. The urine showed increasing amounts of bile, with a ++ to +++ test for albumin and considerable sugar during intravenous glucose therapy. The patient had frequent chills, with occasional fever, while receiving amino acids (Amigen) intravenously. The size of the liver remained unchanged, but it became more tender.

During the third week the patient developed a mousy odor to her breath and the jaundice deepened, with the appearance of dullness and rales at both bases, ascites and sacral edema. She became depressed, stuporous and finally semicomatose, with an erratic temperature and pulse. She had three days of subnormal temperature and expired quietly on the twenty-third day.

#### DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB: Here is a woman who had epigastric fullness and discomfort, which suggest increased portal pressure because of the association with occasional gastrointestinal bleeding. The record implies that there was nothing wrong above the diaphragm and that all the difficulty lay in the abdomen. We are dealing with a large liver, possibly an enlarged spleen and an epigastric mass.

I should like to see the x-ray films, with particular reference to the epigastric mass that is mentioned, as well as the condition of the bones. My interest in the bones is based on the extraordinary albumin-globulin ratio, which discloses such a high level of globulin that one must consider the presence of multiple myeloma.

DR. MILFORD D. SCHULZ: These films show the liver edge extending below the crest of the ilium. The right kidney apparently has rotated and overlies the crest of the ilium.

DR. AUB: You see no evidence of the epigastric mass?

DR. SCHULZ: No. The spleen does not seem large; you can see its tip about where that of the normal spleen usually appears.

I do not believe that the chest is normal. There is something in the right apex. I cannot be sure whether it is in the lung or in the pleura. It is what has been called thickened apical pleura, but may represent atelectasis in the upper lobe. The bones, so far as one can see, are quite all right.

DR. AUB: The patient had an erratic temperature, which suggests sepsis. One or two times it went up to 104°F., apparently owing to the injection of amino acids.

Here then is a woman with a fever, who had had symptoms for five years, and who entered the hospital with a big liver and no intense amount of liver damage. The liver deteriorated rapidly, according to the history, and she died with evidence

of severe liver damage. I think that one can rule out obstructive jaundice or difficulty with the bile ducts on that basis. I believe that this woman had severe damage to the hepatic cells themselves, and that she died of cholemia.

The albumin-globulin ratio in the blood interested me, for there was a high total protein, made up mostly of globulin, the albumin being extremely low. One must discuss four diagnoses: myeloma, amyloidosis, hemochromatosis and cirrhosis.

This woman had severe liver damage, but the blood changes were so marked that one wonders whether they could have been due to liver damage. The alternative is to think of myelomatous lesions in the bones. Bone lesions are not essential, however, since this tumor may be found only in the liver. Later in the disease she had a great deal of albuminuria but no Bence-Jones protein in the urine. There is also the queer finding of a couple of metamyelocytes in the blood, which might have been a misdiagnosis of the plasma cells found in multiple myeloma. I should like to make a diagnosis of multiple myeloma but it is unwise to do so, because it is a rare disease and because there is not enough evidence for it in this record.

The next thing that occurred to me was amyloid disease. Albumin in the urine, without abnormality of the sediment, always suggests amyloid disease to me. Was a Congo red test done?

DR. BENJAMIN CASTLEMAN: No.

DR. AUB: The spleen was not particularly large, but I have seen many cases of amyloid disease in which there was no justification for making the diagnosis. It is an interesting point, but without the Congo red test I am incapable of making the diagnosis.

This record does not contain evidence of jaundice sufficiently severe to justify the diagnosis of acute yellow atrophy of the liver. In other words, the diagnosis that must be made involves a big liver that was not functioning. It could have been a fatty liver, early in cirrhosis, but I do not believe that that is likely. She had several other noteworthy findings, namely, an extremely low cholesterol and no cholesterol esters in the blood, which imply severe liver damage, and a normal phosphatase, indicating, however, that the liver cells were not being rapidly destroyed. Amyloid disease should be entertained as a serious possibility.

In favor of hemochromatosis is the sugar in the urine even though the blood-sugar level is not given.

DR. CHESTER M. JONES: But that was following intravenous glucose therapy.

DR. AUB: The urine is reported to have given a green reaction with Benedict's solution on entrance to the hospital, but this is not adequate evidence for hemochromatosis.

The fourth thing is cirrhosis. I think that she had a mild cirrhosis, not enough to give ascites and therefore not a severe cirrhosis. With an albumin-

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31221

#### PRESENTATION OF CASE

A fifty-five-year-old Polish woman was admitted to the hospital complaining of anorexia, weakness and intractable vomiting.

For the past ten years she had had vague epigastric discomfort, with a feeling of tightness across the abdomen. During this same period she took laxatives frequently for constipation. There had been insidious weight loss for probably a long period. During the past five years the epigastric discomfort had become distressing, with occasional nausea and vomiting. For the past four years there had been infrequent episodes of bright-red bleeding from the rectum. About one and a half months before admission she began to vomit frequently. The vomiting was preceded by epigastric distress varying from a feeling of fullness to moderately severe pain. Vomiting always brought relief. Malaise was pronounced during the month before entry. For about three weeks she had coughed up small amounts of bright blood on occasions.

She had had pneumonia one year before admission, from which she recovered uneventfully. She was seven years postmenopausal.

Physical examination revealed a pale, thin, slightly icteric woman with evidence of a moderate amount of recent weight loss. Many teeth were absent, and the remainder carious. The heart size and rhythm were normal. A mild systolic murmur was heard at the apex. The lungs were clear and resonant. The abdomen was flat. There was a

moderately enlarged, tender liver, extending five fingerbreadths below the costal margin. On inspiration a questionable, firm, tender mass was felt in the epigastrium. The tip of the spleen was just palpable beneath the costal margin on inspiration. Pelvic and rectal examinations were negative.

The temperature was 101°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 65 diastolic.

Examination of the blood showed a white-cell count of 11,000, with 64 per cent neutrophils, 28 per cent lymphocytes, 6 per cent monocytes and 2 to 3 per cent of what were thought to be metamyelocytes. Examination of the urine showed a specific gravity of 1.030; it contained no albumin, and a test for sugar was green to orange with Benedict's solution. The sediment showed an occasional red and white cell. The stool was guaiac negative. A Hinton tset was negative. The serum protein was 7.95 gm. per 100 cc., with an albumin-globulin ratio of 0.5. The chloride, nonprotein nitrogen and van den Bergh test were normal. The phosphorus was 2.7 mg. per 100 cc., and the alkaline phosphatase 2.1 Bodansky units. The prothrombin time was 35 seconds (normal, 18 to 20 seconds).

X-ray examination of the chest and a gastrointestinal series were normal. An intravenous pyelogram showed a large liver extending to the level of the iliac crest. The right kidney was unusually low in position but was normal in shape and function; the left kidney was normal. A barium enema showed the hepatic flexure to lie extremely low in the abdomen. Proctoscopic examination showed intrinsic disease of the rectum and lower sigmoid.

On the first day the patient passed a small blood clot with her bowel movement, but no bright blood, the stool was of normal color. Occasionally she vomited bile-stained material. Further serum studies a week after admission showed a total protein value of 7.16 gm. per 100 cc., with an albumin-globulin ratio of 0.28. The cholesterol value was 53 mg. per 100 cc., with esters too low to read. The van den Bergh reaction was 17.6 mg. per 100 cc. direct and 28.4 mg. indirect. The cephalin flocculation test was ++++, and the prothrombin time 49 seconds (normal, 18 to 20 seconds); later the prothrombin time increased to 54 seconds. The white-cell count

\*On leave of absence.



mediate cause of death, the certificates having been returned. It seems to me that we see a great many persons in whom, without an autopsy, it is impossible to make a diagnosis of the exact type of underlying liver disease and yet the cause of death is undoubtedly hepatic failure. There is an occasional tendency to say that this should be called acute yellow atrophy. In some cases there is a lot of destruction of liver cells, and in others, diffuse carcinomatosis or a similar infiltrative process. One can get this picture with cholemia and yet have no appreciable amount of necrosis. I think that hepatic failure is a good descriptive term for such a final event, just as uremia is in a patient with renal disease.

### CASE 31222

#### PRESENTATION OF CASE

*First admission.* A fifty-five-year-old business man was admitted to the hospital because of jaundice.

He appeared to be in excellent health until three weeks before admission, when he noticed that his urine had become dark, and his stools pale slate colored. The following week he developed anorexia and had frequent soft stools. The urine remained dark and the stools clay-colored until admission. Twelve days before entry it was first observed that he was jaundiced. He felt fairly well and on the following day played tennis; a day later he developed slight nausea. No pain, malaise, chills or fever was noted at any time. He was examined by his physician ten days before he was admitted. At that time the temperature, pulse and respirations were normal. There was marked icterus of the skin and scleras. He had lost no weight recently. The abdomen was negative. The liver and spleen could not be felt. An x-ray examination revealed no gallstones. The stool was negative for bile, and a cephalin-flocculation test was negative. The icteric index was 42 units. He was placed on a high-carbohydrate, low-fat diet supplemented with vitamins. The patient insisted on continuing his work at the office, where he worked until noon each day. During the week before admission he had three soft clay-colored stools a day and lost approximately 10 pounds in weight.

Six years before admission he had an "ulcer," which recurred a year before admission; both times he responded well to medical therapy. His bowel habits had been normal.

Physical examination revealed a well-developed, fairly thin man who was deeply jaundiced but not bronzed. There was no lymphadenopathy. The lungs were clear, with good expansion. The right half of the diaphragm was quite high. The heart was normal in size, rate, rhythm and sounds. The liver edge could be felt three to four fingerbreadths below the costal margin; it was smooth, rounded and nontender. The spleen was not felt. There was

no ascites or edema. Rectal and neurologic examinations were negative.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 80 diastolic.

The urine was dark, with a specific gravity of 1.026, gave a +++ test for bile, and showed traces of albumin and sugar, with an occasional white cell, red cell and cast in the sediment; the test for urobilinogen was plus in dilution of 1:8. Examination of the blood showed 4,400,000 red cells, with 90 per cent hemoglobin (Sahli), and 8500 white cells. The stool was clay-colored and guaiac negative and contained no bile. The van den Bergh reaction was 11.8 mg. per 100 cc. direct, and 16.7 mg. indirect. The serum nonprotein nitrogen and protein and the prothrombin time were normal. The phosphorus was 3.0 mg. per 100 cc. The alkaline phosphatase was 10.2 units per 100 cc., and a cephalin-flocculation test was negative in forty-five hours.

X-ray examination of the gastrointestinal tract revealed the esophagus to be normal. The stomach contained a moderate amount of secretion and showed slight thickening of the mucosal folds. The duodenal cap was slightly deformed, without definite evidence of a crater. The remainder of the duodenal loop showed no evidence of a pressure defect. The liver appeared slightly enlarged, and the spleen normal. At six hours the barium was in the proximal colon. There were a few calcified nodes in the midportion of the abdomen.

The patient had a poor appetite, but with supplementary intravenous feedings he was maintained on a high-carbohydrate, high-protein, high-vitamin and low-fat diet. He was given an ampule of Hykinone each week. After three weeks his stool became somewhat darker and contained a small amount of bile. The van den Bergh reaction dropped to 9.0 mg. per 100 cc. direct, and 12.4 mg. indirect. The alkaline phosphatase fell to 6.4 units, and the test for urobilinogen in the urine was positive in dilutions up to 1:100.

After four weeks in the hospital the patient was discharged to his home under close observation and with a carefully selected diet. The temperature, pulse and respirations had remained normal, but he had lost 5 pounds and his icterus had not noticeably diminished.

*Second admission* (nineteen days later). In the interim he had become stronger; he walked about a mile each day but had lost 3 more pounds. His chief complaint during this time was heartburn, which usually came on several hours after meals. There was no nausea, and he was never awakened from sleep. Three days before admission he vomited for the first time, shortly after drinking a glassful of water. The vomitus contained only the fluid that he had recently drunk. On the following evening he again vomited. He spoke of vague, nonradiating discomfort in the epigastrium.



globulin ratio such as she exhibited there must have been little cirrhosis. Severe cirrhosis should give quite marked ascites, because most of the osmotic pressure in the blood is produced by albumin rather than by globulin. With the evidence in the history suggesting a high portal pressure I think one should make a diagnosis of a mild degree of some form of cirrhosis.

One ends up with the question whether she had a tumor. On the basis of mild cirrhosis she could have had multiple liver-cell carcinomas or hepatomas, accompanied by so-called "carcinomatous cirrhosis." That is a perfectly good diagnosis and would explain the fever, because most patients with carcinoma of the liver have a fever, usually from necrosis in the center of the tumor. Such tumors may be myelomatous.

I can make one definite diagnosis, saying that this patient died of severe liver damage, cholemia, in spite of a large liver. I believe that she had a mild degree of cirrhosis. The other diagnosis lies between those that I have mentioned and cannot, I think, be stated with conviction, but I favor a diagnosis of multiple hepatomas.

DR. PAUL C. ZAMECNIK: Our impression was that the patient had Laennec's cirrhosis to begin with, even though there was no evidence of alcohol ingestion. We also thought that she had a superimposed toxic hepatitis or subacute yellow atrophy.

DR. AUB: I did not discuss that possibility because I thought that the slight degree of jaundice on entrance was much against that diagnosis.

DR. ZAMECNIK: It is interesting that during hospitalization she was able to take little by mouth and was largely fed intravenously. As our efforts failed, we decided to try amino acids. Certain members of the staff suggested that in the face of a failing liver amino acids might be an additional burden. Our experience in giving amino acids for a day or two was that the patient's temperature rose and the jaundice deepened, so that we discontinued this therapy, believing that it did her no good.

DR. JONES: I should like to comment on one remark that Dr. Aub made relative to amyloid disease. I do not believe that I have ever seen a case of amyloid disease with hepatic failure and this degree of jaundice. If it occurs, I am not familiar with it. It would not have occurred to me as a possibility. I should think that one would have to include metastatic disease, and I wonder whether metastatic lesions of a cancer of the pancreas ought to be considered.

#### CLINICAL DIAGNOSIS

Portal cirrhosis, with superimposed toxic hepatitis.

#### DR. AUB'S DIAGNOSES

Cholemia, due to liver cell destruction.  
Cirrhosis of liver, mild.  
Multiple liver-cell carcinoma.

#### ANATOMICAL DIAGNOSES

##### Acute hepatitis.

Portal cirrhosis?

Bile nephrosis.

Ascites.

Splenomegaly.

Pulmonary tuberculosis, old.

Tuberculous ulcer of ileum.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The liver weighed slightly under 1500 gm. and was extremely tough. One could not put one's finger through the parenchyma, even with the fingernail, indicating the presence of a large amount of connective tissue. It was yellow to greenish brown, with scattered areas of fibrosis. Although the liver was fibrotic, there was no granularity of the surface. One could not make out individual nodules of regeneration on the surface, such as are found in portal cirrhosis. There were also a large number of yellow-orange areas that we believed were foci of necrosis.

Microscopical examination showed few remaining normal liver cells. Most cells were large, swollen and necrotic. Many near the areas of degeneration had four or five nuclei in them, a finding indicating active regeneration or hyperplasia of the liver cells. These multinucleated cells were observed in many of the cases of epidemic jaundice recently reported by Lucké.\* In many of the portal areas that could be identified there were lymphocytic and polymorphonuclear infiltration and definite fibrosis. There was in this case, therefore, a severe, acute hepatitis that might be likened to that in cases of epidemic jaundice and that may have been due to a virus or a toxin of some sort. This patient's illness was of ten weeks' duration and I do not believe that so much fibrosis could have been produced in that time. I suppose one has to assume, as Dr. Aub did, that there was an underlying disease that had existed for years, probably a mild cirrhosis. I have recently shown these slides to Lieutenant Colonel Tracy B. Mallory, who believes that this amount of fibrosis can be produced in as short a period as ten weeks. If that is so, we do not have to assume an underlying cirrhosis. The toughness of the gross specimen, however, is in keeping with an old process, which lessened the chances of recovery.

The kidneys were large, weighing 700 gm., and showed a bile nephrosis. The peritoneal cavity contained 1500 cc. of yellowish fluid. The spleen was about twice the normal size, weighing 350 gm.

The lesion in the right apex of the lung proved to be old tuberculosis. The cause for the blood in the stools was a tuberculous ulcer, 1 cm. in diameter, in the terminal ileum.

DR. JONES: More than once there has been objection to the term "hepatic failure" as the im-

\*Lucké, B. Pathology of fatal epidemic hepatitis. *Am. J. Path.* 20:471-593, 1944.

vading and destroying the anatomic relations in that region without giving a big palpable mass. But against that again is the absence of a long story of gall-bladder disease, because gallstones nearly always precede cholecystic carcinoma by twenty-five years or more.

As we go on in the story we find that the patient did begin to have epigastric pain and to vomit. It is also important to notice that the duodenal loop was not widened, because if we grant that there was a tumor well down in the ductal system it would not be surprising to find some abnormality by x-ray in that region. There is some flattening in the upper end of the duodenal loop, and I do not know whether to take that as evidence of an extrinsic mass. I assume that Dr. Schulz does not feel that way about it, and furthermore no mass was palpable. The stools were guaiac negative on many occasions, which is suggestive evidence at least that the patient did not have a tumor low in the ductal system, because the papilla of Vater tumor often gives a guaiac-positive stool when it ulcerates, even if it is only a tiny ulceration at the duodenal entrance of the duct. So, although his pain was minimal, I think the facts that the degree of obstruction fluctuated, that he had no palpable gall bladder and that he later had some epigastric discomfort and vomiting are in favor of obstruction due to stone. He had some weight loss, it is true; but I think we can and do see that in prolonged common-duct obstruction from any cause.

DR. CHESTER M. JONES: I saw this man in consultation. In taking the history I got the story of an abrupt onset of gastrointestinal symptoms, followed about a week later by jaundice, anorexia and nausea. He was clear in telling the story to me, and he gave an excellent story of infectious hepatitis. The thing that was difficult for me to understand at the time was that he had had jaundice for many weeks without the slightest enlargement of the spleen, either then or subsequently. That to my mind is always a disturbing finding, because serious infection of the liver is frequently associated with moderate splenic enlargement. Even though one cannot feel the spleen it usually can be percussed or demonstrated by x-ray. The x-ray films gave no suggestion of enlargement of the spleen. When one cannot demonstrate that finding, the diagnosis of infectious hepatitis always should be treated with a good deal of reservation.

DR. MOORE: How about the normal temperature?

DR. JONES: These patients usually have normal temperatures when jaundice sets in. Only a small proportion of them run a fever.

Our reasoning was similar to that of Dr. Moore, and we believed that the patient's disease was not running true to form, although for at least several weeks he really improved—the jaundice diminished, there was more bile in the stools, and it looked as if he were on the mend. Because he did not get

beyond that point we thought that we had no right to postpone operation any longer. We decided on exploration. The family was told that he might have either carcinoma or gallstones.

#### CLINICAL DIAGNOSIS

Choledocholithiasis?

Carcinoma of bile duct or pancreas?

#### DR. MOORE'S DIAGNOSIS

Choledocholithiasis.

#### ANATOMICAL DIAGNOSIS

Adenoacanthoma of pancreas.

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: I am sorry that Dr. Arthur W. Allen is not here to describe the operation. At exploration he found a greatly distended gall bladder filled with bile. There were no stones in the gall bladder, and he could not feel any in the common duct. He did feel a large hard mass in the head of the pancreas, which was not definitely neoplastic or inflammatory. On the chance that it was a tumor, a cholecystostomy and jejunostomy were performed in preparation for a pancreatoduodenal resection to be done later. A biopsy was not taken because the lesion was too deep within the pancreas.

About three weeks later Dr. Allen resected the head of the pancreas and duodenum. At that time he noticed that the liver, which had been quite swollen and large at the first operation, had shrunk somewhat and that the mass in the pancreas seemed to be much larger than formerly; in fact, he was sure that the mass was a cancer. We did a frozen section and made a diagnosis of carcinoma. Unfortunately the tumor had spread into the body of the pancreas and was quite adherent to the portal vein, hepatic artery and superior mesenteric vein. Resection was carried through the body of the pancreas, but it was thought that all the tumor had not been removed. The carcinoma proved to be an adenoacanthoma, that is, an adenocarcinoma in which some of the epithelial cells had undergone squamous-cell change.

The patient did fairly well for a while but died four months following the operation. At autopsy we found that the tumor had extended down to the tail of the pancreas and that there were metastases in the liver, which were not present at the time of operation, and also in the lungs.

The patient died of cholemia and bronchopneumonia. He was extremely jaundiced. The tumor had invaded around the anastomosis, with ulcerations into the jejunum.

DR. MOORE: Had anyone ever felt a big distended gall bladder?

DR. JONES: We tried again and again, but no one ever felt it.

Physical examination showed no significant change. His icterus, nutritional status and sense of well-being were essentially the same. The liver was five fingerbreadths below the costal margin, and the spleen was not felt.

The urine gave a + test for albumin and a ++++ test for bile; the sediment contained an occasional white cell. The hemoglobin (photoelectric method), which had been 14.3 gm. at the time of discharge, was 12.8 gm. The white-cell count and differential were normal. The stool was clay-colored and guaiac negative and contained no bile. The prothrombin time was normal, but a cephalin-flocculation test was ++++ in twenty-four hours. The alkaline phosphatase was 7.8 units per 100 cc., and the van den Bergh reaction 9.28 mg. direct and 13.2 mg. indirect. The urobilinogen in the urine was positive in a dilution of 1:40.

A week after admission the alkaline phosphatase was 9.6 units per 100 cc. and the cephalin flocculation was negative. His diet was supplemented by intravenous feedings, and he received three transfusions. During one transfusion he had a chill and the temperature spiked to 101°F., otherwise the temperature, pulse and respiration remained normal. A laparotomy was performed on the twelfth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. FRANCIS D. MOORE: This case seems to me to contain elements suggesting various pathologic lesions. If one reads through most of the case one would say that the jaundice was painless, but then this must be qualified because later the patient did have some discomfort, characterized as epigastric pain. The jaundice was fluctuating. So it was fluctuating, obstructive, "almost painless" jaundice.

May we see the x-ray films? The main thing that I should like to find out from Dr. Schulz is whether this man did have an ulcer, or whether it was gall-bladder disease that the patient or his physician thought was an ulcer.

DR. MILFORD D. SCHULZ: I think that he probably had an ulcer. The duodenal bulb is flat and slightly irregular. I do not believe there is anything shown by the films beyond what has been stated in the protocol.

DR. MOORE: He has no opaque gall stones, a little duodenal deformity but nothing striking and no widening of the duodenal loop, which is important.

Was the jaundice primarily obstructive, not being due to intrahepatic disease or excessive hemolysis? I think that it probably was. The direct to indirect ratio of the van den Bergh reaction was about 75 per cent, which favors such a diagnosis: this interpretation is not infallible, but in this hospital over a period of time it has been fairly reliable. The highest direct to indirect ratio was the first one obtained. Later, the patient apparently developed liver damage, as evidenced by the positive cephalin-

flocculation test and also by a change in the ratio of the direct to indirect bilirubin in the direction characteristic of parenchymatous liver disease. The alkaline phosphatase was elevated on several occasions, which is in favor of obstructive jaundice. There was little urobilinogen in the urine when the patient was first admitted. Later it was high, and during the second admission it was about halfway between. To get urobilinogen in the urine there must be urobilinogen in the feces. This patient had urobilinogen in the urine at a time when he had a bile-free stool. That finding is inconsistent, but the amounts present do not support the idea that it was a hemolytic process, nor do the red-cell counts recorded in the protocol.

Can we dismiss an acute hepatitis? I think we can. The patient did not have fever. His liver enlarged slowly. When first seen, the liver was not large or tender, which I think is unusual for acute hepatitis, and he had clay-colored stools right from the start, even antedating the jaundice. He had a negative cephalin-flocculation test on the first admission, suggesting that early in the disease the liver cells were not working under too great a burden. Just before operation, the cephalin-flocculation test changed from positive to negative in a short time. I do not know enough about the test to be sure that that is suggestive of a change in status. I should rather believe that it was a laboratory phenomenon.

Then there are portal cirrhosis of the liver and one of its precursors to be considered. Against these are the facts that he had not developed ascites, that the serum was normal and that he had no esophageal varices.

So, narrowing ourselves down to obstructive phenomena of one sort or another, we have tumor on the one hand and stones on the other. Tumor usually produces a story of increasing jaundice that does not fluctuate. This man had definite fluctuation of bile in the stools and of his jaundice, suggesting that the obstruction let up for a while. That is in favor of a stone. In favor of tumor, however, is the relatively rapid onset in a man of fifty-five, with apparently little previous history of disease of any sort unless the ulcer story was really gall-bladder disease.

One other fact that I think is important is that he did not have a palpable gall bladder. If the obstructive jaundice had been due to neoplasm involving the biliary tree from the junction of the cystic and common ducts downward we should expect him to have developed a big, soft, nontender, palpable gall bladder. The fact that he did not have that in the presence of jaundice, which was apparently obstructive, suggests that it was due to stone and that the reason the gall bladder did not enlarge was that it was involved in old chronic cholecystitis. One might argue the other way, and say that he had carcinoma of the gall bladder, which is capable of in-

pected the human serums used in the preparation of the vaccines. Their suspicion was strengthened by the fact that all the icterogenic lots contained serum from donors who had previously suffered from catarrhal jaundice. It was thought that there was evidence to suggest that a fairly large proportion of normal persons act as carriers of the icterogenic agent, which they assumed to be a virus. They made numerous attempts to isolate the causative agent by inoculation of various experimental animals with the incriminated vaccines or with blood, tissues or excreta from jaundice patients. Their studies gave only negative or, at most, suggestive results.

A thorough pathological study based on 125 fatal cases of hepatitis that occurred in the United States Army during 1942 and made by Lieutenant Colonel Balduin Lucké,<sup>4</sup> of the Army Medical Museum, has recently been published. Many photographs of the gross and microscopical findings in the liver are shown, some of them in color. The findings were essentially those of yellow atrophy of the liver. The mechanism of the jaundice was considered to be obstruction of the lobular canaliculi. Cerebral lesions, consisting of an acute nonspecific degeneration of ganglion cells and a mild meningoencephalitis, were found in 5 per cent of the cases and were believed to be due to a loss of the detoxifying functions of the liver. The exact nature of either lesion, however, is not known.

In another paper, Lucké<sup>5</sup> presents the pathological findings in 14 patients who recovered from typical hepatitis during the epidemic and subsequently died or were operated on. In 6 of the cases death resulted from traumatic accidents, and 6 of the other deaths were due to unrelated diseases. In the 2 remaining cases a fragment of liver was removed in the course of an operation. The tissues were obtained from one to fourteen months after clinical recovery from the jaundice. In those who died from intercurrent diseases during convalescence or within a month after clinical recovery, the liver lobules were mostly reconstituted but there was still some evidence of the previous damage. In those examined more than one month after recovery, the liver parenchyma was completely restored without significant scarring and with only traces of the previous damage found in the portal areas; no evidence

of permanent hepatic damage was found. It is well to mention, however, that these cases did not include any in which symptoms were prolonged for many months, as has been noted in some of the cases of post-inoculation jaundice. It is possible that in such cases considerable pathologic changes may persist.

Additional investigations concerning the etiology of these types of jaundice have also been recently reported. Neefe and his coworkers<sup>6</sup> succeeded in producing hepatitis in each one of 9 volunteers. In some of the subjects there were definite symptoms accompanied by jaundice, whereas in others there was demonstrable hepatitis by laboratory tests although clinical jaundice did not appear. In 5 of these subjects pooled mumps convalescent plasma was used; 4 of them developed hepatitis with jaundice, and the fifth showed laboratory evidence of mild hepatitis without jaundice. Two more received intravenous injections of plasma from one of the previous group twenty-five days after inoculation, and both developed mild hepatitis without jaundice; the donor of the plasma developed jaundice eighty-seven days after the plasma was obtained. Two more volunteers were given subcutaneous inoculations of a lot of yellow-fever vaccine known to be icterogenic, and both developed hepatitis, one with and the other without jaundice. One of the volunteers was reinoculated with the same material after recovery but remained free of disease during one hundred and forty days of observation. The onset of the disease in 6 of these 9 cases occurred twelve to thirty-five days after inoculation, which is a considerably shorter incubation period than that in most of the cases of post-vaccination or other types of homologous serum jaundice. There were 2 cases of jaundice that may have resulted from contact with one of the volunteers.

Some of the earlier studies of Findlay and his colleagues, particularly those concerned with the transmission of post-inoculation jaundice by means of intranasal inoculation, were referred to in a previous editorial.<sup>2</sup> More recently these workers<sup>7</sup> have reviewed the clinical findings in 689 cases of jaundice that occurred in the British Army. They have also presented immunologic and epidemiologic

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## INFECTIOUS HEPATITIS

CASES of epidemic jaundice and of homologous serum jaundice continue to attract a great deal of attention, large numbers still being encountered both in military practice and in the civilian population. Although deaths are relatively few, the disease is of considerable importance. Even in mild cases there is usually an acute illness that lasts about three or more weeks, and convalescence may be quite prolonged before there is a complete return to normal. Among American troops, particularly in cases that followed inoculation with yellow-fever vaccines containing the icterogenic agent, serious disabling sequelae of various sorts have been encountered. Interest in this subject therefore is

great; intensive investigations have recently been made, and many are still in progress. Attention has already been called in these columns to some of the significant work that has contributed to an understanding of such conditions.<sup>1, 2</sup> A few of the more recent contributions have shed further light on this perplexing problem.

One of these studies is contained in a report to the Surgeon General of the United States Army by a special group of workers who investigated the cases of jaundice among Army personnel in the western region of the United States and their relation to vaccination against yellow fever.<sup>3</sup> Cases occurred in this area throughout 1942, but the main outbreak began in March and continued through July, with two peaks during that period. There had been a few small outbreaks of jaundice among civilians in California before the cases occurred in the Army, but the civilian cases could not have given rise to the widespread epidemics in the military personnel. It was more difficult, however, to determine whether some of the later cases in the Army might not have resulted from the earlier outbreaks.

In agreement with the results of many other workers, the jaundice in the Army personnel was traced to vaccination against yellow fever and particularly to a number of lots of vaccine, all of which contained the same human serum. The jaundice began in most cases from thirteen to sixteen weeks after the vaccination. Cases among unvaccinated individuals were scattered throughout the year, and in that respect they resembled the cases that occurred in men who were vaccinated with nonicterogenic lots of yellow-fever vaccine. The occurrence of such cases extended over a period of seventy-eight weeks after vaccination. The case fatality rate was 3 per 1000 among the patients with hepatitis who received the icterogenic lots of vaccine. It is of interest that, as a matter of chance, no icterogenic lots of vaccine had been used in foreign countries and in the Navy at the time of these investigations.

From their own studies these workers were not able to determine which of the various materials used in the preparation of yellow-fever vaccine actually contained the agent responsible for the outbreak of the post-vaccination jaundice. On the basis of the findings of others, however, they sus-

feces from both spontaneous and post-inoculation cases. The incubation period varied from twenty to eighty-four days, averaging thirty-seven. One case of moderately severe jaundice appeared among the uninoculated personnel of that institution fifty-one days after the beginning of the experiment and thirty-one days after the first experimental case had developed. At another institution 3 of 5 volunteers developed hepatitis from fifty to seventy days after the intracutaneous inoculation of icterogenic serum. In another series of feeding experiments the incubation period was found to be twenty-eight days,<sup>12</sup> which is considerably shorter than that after the inoculation of icterogenic serums.

The results of various transmission experiments are reviewed by MacCallum and others.<sup>13</sup> Transmission to pigs has been claimed by Danish workers, and the infection of chick embryos and canaries with materials from human cases has been reported by German investigators, but these results have not been confirmed. In man the disease has been produced by serum, duodenal juice, urine and feces from cases of infectious hepatitis and by serum and nasal washings from cases of homologous serum jaundice. It is also claimed that the jaundice resulting from arsenotherapy may result from traces of serum left in the syringe from previous injections of other patients who harbored the infectious agent. The latter possibility is rendered plausible by the experience of Bradley et al.,<sup>14</sup> who observed an outbreak of homologous serum jaundice involving 57 per cent of persons injected with a particular batch of pooled human serum that was being used in a study of allergic reactions. Jaundice resulted from doses varying from 0.1 to 1200 cc. Neither the incubation period, which varied from forty-five to one hundred and four days, nor the severity of the jaundice was related to the size of the dose.

All these observations are of considerable interest, but many important problems still remain unsolved. It is to be expected that current investigations will shed further light on the etiologic agent and on many of the clinical features of this disease. In the meantime it is obvious that one is dealing with a serious infection caused by a fairly sturdy agent, which is transmissible through inoculation, as well as through natural channels, and

which may persist for considerable periods in the patient. The most obvious implication is that blood banks should refuse to accept as donors persons who have had an attack of infective hepatitis within a few months — possibly within a year. To obtain more information concerning the occurrence and spread of this important disease it is also imperative that it be made reportable. Such facts could then be applied to the control and prevention of the disease. In this connection, the possible value of gamma globulin in the prevention and modification of the disease is now under investigation.

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## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

CHESBRO — Lt. Comdr. Wallace L. Chesbro, formerly of Springfield, was killed on April 28 when the hospital ship, *U. S. S. Comfort*, was attacked by a Japanese suicide pilot off the coast of Okinawa. He was in his thirty-third year.

Dr. Chesbro received his degree from Tufts College Medical School in 1938. He was a fellow of the American Medical Association.

His widow, his daughter, his mother and two brothers survive.

HAVILAND — Walter C. Haviland, M.D., of Mansfield Depot, Connecticut, died May 14. He was in his sixty-fourth year.

Dr. Haviland received his degree from Baltimore Medical College shortly before he moved to Worcester in 1904. He became superintendent of the Herbert Hall Hospital in 1912, and on May 10, 1932, was appointed to the Worcester Board of Health. In 1934 he left Worcester to take a position at

observations purporting to show that post-vaccination jaundice, that is, homologous serum jaundice and infectious hepatitis or catarrhal jaundice, are caused by the same or closely related agents. This conclusion is based on three types of evidence. In the first place, they present case histories that suggest the spread of post-vaccination jaundice to contacts who had not been inoculated. Secondly, they ascertained the incidence of infectious hepatitis earlier in life among a sample of British officers and enlisted men and deduced from their findings that a previous attack of infectious hepatitis gave some, although not absolute, protection against post-inoculation jaundice. Finally, in complement-fixation tests with an antigen prepared from the liver of a patient who died of post-inoculation jaundice they obtained positive results with convalescent serums from patients with post-inoculation jaundice and also from patients with infectious hepatitis who had not been vaccinated. The complement-fixation test was not specific, however, giving positive results with serums from cases of arsenical hepatitis and yellow fever. The antigen responsible for the complement-fixation was not considered to be the agent responsible for the jaundice, since they obtained no positive takes following its inoculation. They also point out that hepatitis can occur without jaundice since positive complement-fixation tests were obtained in certain persons who gave no history of jaundice. They carried out additional transmission experiments, which, however, were mostly unsuccessful.

From a study of the answers to questionnaires among British officers and enlisted men these investigators obtained a history of catarrhal jaundice in 6.3 per cent of the 2614 men who replied. Only 4 men, or 2.6 per cent, of those with positive histories had a second attack, the period intervening ranging from one and a half to fifteen years. Among the 689 cases of hepatitis that they analyzed, relapses occurred in 14, or about 2 per cent, which is an incidence quite similar to that of those with a second attack of catarrhal jaundice.

A case reported by Neefe et al.<sup>8</sup> is of interest with respect to the relation of the two types of jaundice. Their case was one of a severe and prolonged hepatocellular jaundice following the injection of pooled

mumps convalescent serum. This serum was given because of symptoms suggesting pancreatitis that developed in the course of an attack of mumps acquired by the patient from one of his children. The patient gave a history of having had a characteristic attack of catarrhal jaundice nine years previously. In this connection may be mentioned Hayman and Read's<sup>9</sup> report of an outbreak of 405 cases of jaundice following yellow-fever vaccination observed in an Army hospital between April and September, 1942. Among these cases were 7 in which a history was obtained of "catarrhal jaundice" occurring six months to twenty years previously. One patient stated that he had received yellow-fever vaccine in October, 1939, before going to South America for an oil company and that he developed jaundice in January, 1940, together with a number of other employees of the company. These authors subsequently observed another group of 100 cases of jaundice among troops returning from the combat zone who had had yellow-fever vaccine from twelve to eighteen months previously. Evidence of a short incubation period, suggesting that these were cases of epidemic jaundice or infectious hepatitis, was obtained from 2 cases in nurses. One of them had taken special care of a fatal case nineteen days before she developed jaundice, whereas the other had been "out" with an officer two days before he developed jaundice and became jaundiced after twenty-eight days.

Oliphant<sup>10</sup> attacked the problem more directly by inoculating icterogenic serum subcutaneously into persons convalescent from attacks of jaundice. He observed that recovery from homologous serum jaundice resulted in immunity to reinoculation with serum from acute cases of infectious hepatitis or with icterogenic yellow-fever vaccine. This immunity persisted for at least twelve to eighteen months. On the other hand, pooled serum obtained from one to three months after recovery from homologous serum jaundice, when mixed with icterogenic yellow-fever vaccine, failed to protect 1 of 10 persons who were inoculated with the mixture.

Havens and his co-workers<sup>11</sup> succeeded in transmitting hepatitis to 5 of 9 human volunteers in one institution by feeding specimens of serum, urine or

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## LYMPHOSARCOMA OF THE BOWEL IN CHILDHOOD\*

GEORGE D. CUTLER, M.D.,† RICHARD B. STARK, M.D.,‡ AND H. WILLIAM SCOTT, JR., M.D.§

BOSTON

**P**RIMARY neoplasms of the large or small intestine are extremely rare in childhood as compared with those in adult life. Except for true adenomatous polyps, most intestinal tumors encountered in early life are sarcomatous. Lymphosarcoma is one of the more frequent types of this group, and it is the purpose of this paper to describe our experience with this tumor in children under twelve years of age, as well as a case of reticulum-cell sarcoma.

### **PATHOLOGY**

Lymphosarcoma was separated from the general group of lymphoma in 1893 by Kundrat,<sup>1</sup> who described it as a highly malignant tumor of lymphoid tissue having a fairly uniform cell type. The tumor may arise in the lymph nodes, spleen, tonsils and the lymph follicles of the gastrointestinal tract, and apparently in many organs not usually thought of as containing significant amounts of lymphoid tissue. Extensive studies including reviews of the literature on this subject were reported in 1919 by Graves,<sup>2</sup> in 1932 by Ullman and Abeshouse,<sup>3</sup> in 1940 by Sugarbaker and Craver<sup>4</sup> and in 1942 by Stout.<sup>5</sup>

The controversial subject of the classification and inter-relations of the various types of lymphoma exceeds the scope of this paper. In this regard reference may be made to the work of Gall and Mallory,<sup>6</sup> Jackson,<sup>7</sup> Warren and Picena<sup>8</sup> and Krumbhaar.<sup>9</sup> The close relation between the various manifestations of neoplasia of the lymphocyte and its precursors seems to be quite well established. The confusion in the terminology applied to these tumors is widely known. Gall and Mallory<sup>6</sup> were unable to predict from histologic examination of lymph nodes involved by so-called "lymphocytoma," "lymphoblastoma" or "lymphosarcoma" whether there were accompanying leukemic blood changes.

Certain pathologists apparently believe that the diseases designated by the terms "lymphatic leukemia," "aleukemic lymphatic leukemia," "lymphoblastoma," "lymphocytoma," "reticulum-cell sarcoma" and "lymphosarcoma" are variants of the same fundamental neoplasm.

Regardless of the inter-relation of these conditions, a malignant tumor of the lymphoid tissue may certainly appear as an original focus in the intestinal tract, and may remain temporarily local but ultimately invade and metastasize in a manner closely resembling that of carcinoma. The term "lymphosarcoma" may conveniently be applied to this neoplasm, despite certain theoretical objections.

The tumor arises in the lymphoid follicles of the submucosal layer of the bowel and infiltrates the remaining layers, although tending to remain intramural, and to extend through mucosa and serosa only as a relatively late change. Longitudinal and circumferential subserosal extension may cause diffuse thickening and dilatation of a segment of bowel, giving rise to the so-called "garden hose" appearance. The absence of a well-developed fibrous stroma as in carcinoma accounts for the rarity of the "napkin-ring" constriction of the bowel so frequent in the latter. Yellowish-white, subserosal plaquelike tumors, frequently umbilicated and frequently multiple (Fig. 1), represent a relatively early stage of the process. Since the mucosa is not primarily involved, large fungating masses completely enveloping the bowel may develop before intestinal obstruction is caused (Fig. 5). For the same reason, ulceration due to ischemic necrosis of the mucosa is a late result, in direct contrast to its early appearance in carcinoma. On palpation the lymphosarcomatous mass is softer, more friable and more rubbery than the hard mass of carcinoma.

Elaborate cytologic classifications of the subtypes of lymphoma have been developed by several pathologists.<sup>6-8</sup> For practical purposes two general groups are recognized — lymphosarcoma and reticulum-cell sarcoma. In the first group the type cell is the lymphocyte or lymphoblast. Both groups are characterized microscopically by destruction of normal

\*Read by title at the annual meeting of the New England Surgical Society, Boston, September 20, 1944.

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the Connecticut State Hospital at Middletown, where he stayed five years before going to Mansfield in 1939. He was a member of the American Society of Psychiatrists and the Connecticut State Medical Society and a fellow of the American Medical Association.

His widow, a daughter and three grandchildren survive.

**HIRSCH** — Henry L. Hirsch, M.D., of Springfield, died May 8. He was in his sixty-first year.

Dr. Hirsch received his degree from Jefferson Medical College in 1906. He served on the Springfield School Committee from 1913 to 1920. He was a first lieutenant in the United States Army during World War I. He was a fellow of the American Medical Association.

His widow, two brothers and three sisters survive.

**MAKLER** — Mark Makler, M.D., of Lynn, died May 14. He was in his forty-third year.

Dr. Makler received his degree from Northwestern University Medical School, Chicago, in 1927. He was a member of the staffs of the Children's Hospital, Boston, and of the Lynn Hospital. He was a member of the New England Pediatric Society and a fellow of the American Medical Association.

His widow, two sons, his mother and a sister survive.

**MOORE** — John H. Moore, M.D., of Boston, died February 24. He was in his seventy-sixth year.

Dr. Moore received his degree from Harvard Medical School in 1897. For many years he was medical examiner for the John Hancock Mutual Life Insurance Company.

**THISSELL** — J. Abbott Thissell, M.D., formerly of Beverly, died May 14. He was in his eighty-seventh year.

Dr. Thissell received his degree from Harvard Medical School in 1885. He was formerly a member of the Massachusetts Medical Society.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Lowell	June 1	Albert H. Brewster
Salem	June 4	Paul W. Hugenberger
Haverhill	June 6	William T. Green
Brockton	June 14	George W. Van Gorder
Worcester	June 15	John W. O'Meara
Pittsfield	June 18	Frank A. Slowick
Springfield	June 20	Garry deN. Hough, Jr.
Fall River	June 25	Eugene A. McCarthy
Hyannis	June 26	Paul D. Norton

## MISCELLANY

### NOTE

A new medical society, the New Hampshire Roentgen-Ray Society, was founded a few months ago. The aims of the society are to maintain and improve the standards of x-ray service in that state. Dr. Fred S. Eveleth of Concord was elected president, and Dr. Richard C. Batt, of Berlin, secretary.

## CORRESPONDENCE

### RH FACTOR

To the Editor: The editorial "The Rh Blood Factor" in the April 19 issue of the *Journal* is timely and brings attention to a subject to which physicians as a whole are giving scant regard. Strangely enough, even in Boston, where the Blood Grouping Laboratory directed by Dr. Louis K. Diamond has been most active, most physicians view this subject as being of no practical importance. The editorial, however,

in its attempt to emphasize the practical importance of this subject has possibly conveyed a wrong impression, which I believe was not intended.

In one paragraph the editorial reads, "The practical importance of the Rh factor concerns Rh- women and their Rh+ offsprings." May I disagree that the practical importance of this factor is in pregnancy alone, which is implied in the above quotation. The practical importance of the Rh factor concerns all Rh- people, whether it be man or woman.

To quote further from the editorial: "The inferences are obvious. Rh- persons should not receive repeated transfusions from Rh+ donors." The foregoing statement leads to an erroneous conclusion because of the word "repeated." It implies that one transfusion of Rh+ blood to an Rh- person is of no consequence. Again, the editorial would be much more accurate if it were written, "Rh- persons should not receive any whole-blood transfusions from Rh+ donors." For instance, a young girl long before she enters the stage of puberty may have to receive a whole-blood transfusion for one reason or another. If she is Rh- and is transfused with Rh+ blood and then years later is married to an Rh+ man and becomes pregnant, her first pregnancy may be seriously affected by the transfusion given years before. In other words, such a transfusion sets a stage that years later may seriously affect her and her offspring's health and viability. On the other hand, if an Rh- man or boy, for one reason or another, is given a transfusion of Rh+ blood, that individual may be sensitized for the remainder of his life. At a much later date he may be involved in a serious accident or may have to undergo a major operation in a hospital, either of which may demand an immediate whole-blood transfusion. If in this emergency procedure he is again given Rh+ blood, — and he has an 87 per cent chance of this being so, — he is likely to suffer a transfusion reaction, which may kill him or at best will add insult to injury. Therefore, it is important in every case that an Rh- man, woman or child does not receive Rh+ blood.

I realize that the editorial later explains the phrases and words quoted above, but my point is that most people, if they peruse the editorial page, read the first sentence of a paragraph or at least remember only that part of it and may not read the subsequent sentences and paragraphs.

I believe that calling attention to these statements about whole-blood transfusions will impress your readers to the extent of encouraging changes in their methods and ideas of testing blood prior to transfusion.

WILLIAM FREEMAN, M.D.

Worcester State Hospital  
Worcester, Massachusetts

## NOTICES

### NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, June 7, at 7:15 p.m. in the classroom of the nurses' residence. Mr. Lester W. Dearborn will speak on the subject "Some Psychological Aspects of Frigidity." Dr. Lucile Lord-Heinstein will be chairman.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 7

#### FRIDAY, JUNE 8

\*9:00-10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Mallory Building, Boston City Hospital.

12:00 m.-1:00 p.m. Clinicopathological conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

#### SATURDAY, JUNE 9

\*10:00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

(Notices continued on page xix)

Postoperatively, the patient did fairly well for a short period. After the pathologic diagnosis of lymphosarcoma had been made, it was decided not to do a second-stage resection of the chronic intussusception as planned but to give roentgen-ray therapy alone. Because of delayed wound healing only 600 r of x-ray radiation was given, following which the patient was discharged home on the 35th day, to return for heavy roentgen therapy when the wound was well healed. Because of parental difficulties, however, he did not return for admission but died at home 1 month after discharge. Repeated blood examinations showed no evidence of leukemia.

Microscopical study of an omental biopsy showed diffuse infiltration of omental fat by closely packed lymphocytic cells in no orderly arrangement. There were numerous mitoses. Diagnosis: lymphosarcoma.

CASE 2. E. C. (CH103886), a 7-year-old boy, entered the hospital in December, 1933, because of an abdominal mass noted 2 days previously. He had been well until 3 weeks before admission, when he became anorexic, listless and easily fatigued and complained of vague abdominal pains. The bowels were constipated. There was no vomiting. Two days before entry the family doctor was consulted, who sent the patient to the hospital because of a large mass in the right side of the abdomen.

Physical examination on entry showed a well-developed and well-nourished boy with a protuberant, distended ab-

domen. The stools had been normal. The past history was noncontributory.

Physical examination on admission showed a well-developed and well-nourished baby crying as if with pain. The abdomen was slightly distended, but without tenderness, spasm or a palpable mass. The liver edge and the tip of the spleen were just palpable. The rest of the examination was essentially negative. The urine showed a ++ test for albumin but was otherwise negative. The red-cell count was 4,200,000 and the white-cell count 6000, with 71 per cent neutrophils, 22 per cent lymphocytes, 5 per cent monocytes, and 2 per cent eosinophils. The platelets were normal.

During the first 12 hours on the ward the patient refused feedings and vomited three times. He then began to develop intermittent episodes of abdominal pain with doubling of the knees on the abdomen. Fluoroscopy with a barium swallow revealed dilated loops of small bowel and fluid levels. A diagnosis of intussusception was made and laparotomy was performed. An enteric intussusception of the ileoileal type was present in the distal ileum. This was easily reduced, and the congested bowel quickly regained normal color. The cause of the intussusception was identified as two plaque-like, yellowish, intramural tumors of the intussusceptum measuring 2.5 by 1.5 cm. in diameter, respectively. These were situated on the antimesenteric border of the ileum 3 or 4 cm. apart. This segment of ileum was consequently resected (Fig. 1) and a lateral anastomosis was constructed.

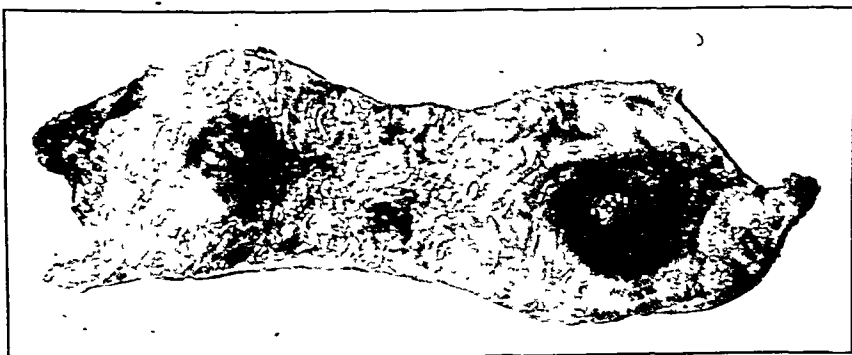


FIGURE 1. Photograph of a Surgically Excised Segment of Ileum Containing Two Intramural Lymphosarcomas That Had Caused Acute Intussusception (Case 3).

domen. There was an enormous hard, nontender mass filling most of the right side of the abdomen, extending from the midline to the midaxillary line and from the costal border into the pelvis. Its lower limit was easily felt by rectum. Aside from additional signs of abdominal fluid the remainder of the examination was essentially normal. Urinalysis was negative. The red-cell count was 4,080,000 and the white-cell count 11,400, with 70 per cent neutrophils and a normal smear. Roentgenograms of the chest showed no metastases.

Laparotomy was carried out with a preoperative diagnosis of abdominal tumor. Opening of the abdomen revealed a grapefruit-sized, whitish-yellow tumor of the cecum and ascending colon. This was diffusely infiltrating and enveloped the large bowel, extending posteriorly to the abdominal wall and medially to the omentum. Several adjacent loops of small bowel were adherent to the mass. The mesenteric lymph nodes were enlarged, rubbery and hard. There was no hope of successful resection. A biopsy of the tumor was performed, and the abdomen was closed.

Postoperatively, the patient had a rapid downhill course. Although he did not become obstructed, he quickly developed marked cachexia. Delayed wound healing prevented early roentgen-ray therapy, and death occurred from terminal pneumonia on the 16th postoperative day. The peripheral blood showed no evidence of lymphatic leukemia.

Microscopical examination of the biopsy specimen showed closely packed masses of lymphoblasts with numerous mitotic figures. Diagnosis: lymphosarcoma.

CASE 3. F. R. (CH264439), a 4-month-old boy was admitted on July 29, 1942, with a 7-day history of irritability and refusal of feedings. In the 24 hours before entry he had

Postoperatively the patient had a stormy course for 5 days, and then passed stools satisfactorily and remained afebrile. Repeated blood smears showed no evidence of lymphatic leukemia. No roentgen-ray therapy was given. The patient was discharged home in apparently good condition on the 18th day. He quickly became listless, irritable, anorexic and pale and developed a petechial rash over the extremities. He was readmitted to the Medical Service 10 days after discharge with a picture of advanced acute lymphoblastic leukemia. The liver and spleen were enlarged as were the cervical lymph nodes. The red-cell count was 2,520,000 and the hemoglobin 6.5 gm. The white-cell count was 76,000, with 4 per cent neutrophils, 3 per cent eosinophils, 4 per cent monocytes, 15 per cent mature lymphocytes and 74 per cent lymphoblasts. No platelets were seen on the smear. Therapy was omitted at the parents' request, and the infant died at home 5 days after the second hospital entry.

Microscopical examination of the intramural tumors of the excised ileum showed diffuse infiltration of bowel wall with masses of cells resembling lymphocytes and less numerous lymphoblasts. Mitoses were frequent. Diagnosis: lymphosarcoma.

CASE 4. J. B. (CH273465), a 26-month-old boy, was admitted on June 5, 1943, because of bloody stools of 25 days' duration. The past history was irrelevant. Except for diminished appetite and failure to gain during the month prior to admission there were no symptoms. Examination by the family physician had revealed a mass in the rectum. Proctoscopy and biopsy had been carried out in another hospital, followed by referral to this hospital with a diagnosis of malignant tumor of the rectum.

nodal architecture, capsular invasion, numerous mitoses and predominance of one of the above cell types.

In our 5 cases of lymphoma arising primarily in the bowel, 2 were of the lymphocytic variety, 2 were lymphoblastic, and 1 was of the reticulum-cell group.

CLINICAL ASPECTS

In a recent ten-year study of histologically verified malignant tumors at the Children's Hospital, Farber<sup>10</sup> found 75 (21 per cent) belonging to the leukemia-lymphoma group. Of these 47 were classified as acute leukemia, 14 as Hodgkin's disease and 14 as lymphosarcoma. Five of these patients had primary tumors of the bowel with symptoms and signs that led to operative intervention. Data of these cases are summarized in Table 1. The youngest

was found to have one of the ileoileal type whose leading point was an intramural lymphosarcoma. Two older patients (Cases 1 and 5) had increasing constipation for four and three months, respectively, leading to fecal impaction. One of these patients developed acute intestinal obstruction a few days after hospitalization and by barium enema was found to have an ileocolic intussusception (Fig. 4) associated with a large tumor of the terminal ileum. The other patient proved to have a chronic colocolic intussusception resulting from lymphosarcoma of the cecum and ascending colon. The presenting complaint in another patient (Case 2) was an essentially asymptomatic irregular abdominal mass filling the right lower quadrant of the abdomen. In the last patient (Case 4), bloody stools attracted attention to a lemon-sized intramural reticulum-cell sarcoma of the rectum (Fig. 2).

TABLE 1. Summary of Data from Five Children with Lymphosarcoma of Bowel.

CASE No.	AGE Yr.	SEX	CLINICAL PICTURE	SITE OF TUMOR	OPERATION	X-RAY THERAPY	TERMINAL LEUKEMIA	COURSE
1	6 4/12	M	Fecal impaction and chronic intussusception	Ascending colon	Ileotransverse colostomy (biopsy)	600 r	?	Died
2	7	M	Abdominal mass	Ascending colon	Laparotomy (biopsy)	None	No	Died
3	4/12	M	Acute intussusception	Terminal ileum	Reduction and resection, with anastomosis	None	Yes	Died
4	2 1/12	M	Melena and rectal mass	Rectum	Abdominoperineal resection	3000 r	No	No recurrence; well for 15 mo.
5	6 6/12	M	Fecal impaction and acute intussusception	Terminal ileum	Mikulicz resection	1350 r	Yes	Died

patient was four months of age and the oldest seven. All were boys. This is in keeping with the male predominance reported in the literature.

The general incidence of lymphosarcoma of the bowel in children may be further illustrated by reports from other clinics. Cave<sup>11</sup> in 1932 found only 1 case in a child among 15 patients observed during a twenty-one-year period at Roosevelt Hospital. McSwain and Beal,<sup>12</sup> reporting 20 cases of lymphosarcoma of the gastrointestinal tract treated at New York Hospital during the last nine years, encountered this tumor in 2 children. Donovan<sup>13</sup> states that only 1 child with enteric lymphosarcoma has been observed in the last fifteen years at the Babies Hospital in New York City.

Ullman and Abeshouse<sup>3</sup> believe that there is no absolutely characteristic clinical picture of this disease. Symptoms may have an insidious onset or may present themselves as an acute abdominal catastrophe. Obviously, the manifestations of disease are more or less dependent on the location of the tumor and the degree of intestinal obstruction it causes. The youngest patient in this series, a four-month-old baby (Case 3), had the classic symptoms of acute intussusception and at operation

The peripheral blood showed no detectable abnormality in any of these 5 patients at the time of admission. Terminally, however, 2 of them developed the blood picture of lymphoblastic leukemia.

CASE REPORTS

CASE 1. W. T. (CH149544), a 6-year-old boy, was admitted in June, 1931, because of intermittent abdominal cramps of 3 months' duration. Four months before entry, appendectomy had been carried out at another hospital for alleged acute appendicitis. Irritability, fatigue and anorexia but no vomiting accompanied the pain. There was increasing constipation, and 10 days before entry a mass was noted in the epigastrium. Physical examination on admission showed a well-developed and well-nourished boy in no acute distress. In the right upper quadrant of the abdomen there was a rounded, firm, non-tender mass 7 cm. in diameter. Hard fecal lumps were palpable in the sigmoid and rectum. The remainder of the examination disclosed nothing remarkable. The urine, blood and stools were normal. After evacuation of the impacted feces by enemas, fluoroscopy of the colon showed a filling defect in the transverse colon suggesting intussusception. A diagnosis of chronic intussusception was made. Laparotomy revealed an irreducible intussusception of the ileocolic type that had passed just beyond the hepatic flexure. There were numerous large rubbery, yellow nodules in the omentum, which was adherent to the ileum and had been drawn into the intussusciptions. The mesenteric nodes were large and firm. Biopsy was taken of the omental nodules, and a short-circuiting lateral anastomosis between proximal ileum and transverse colon was carried out.

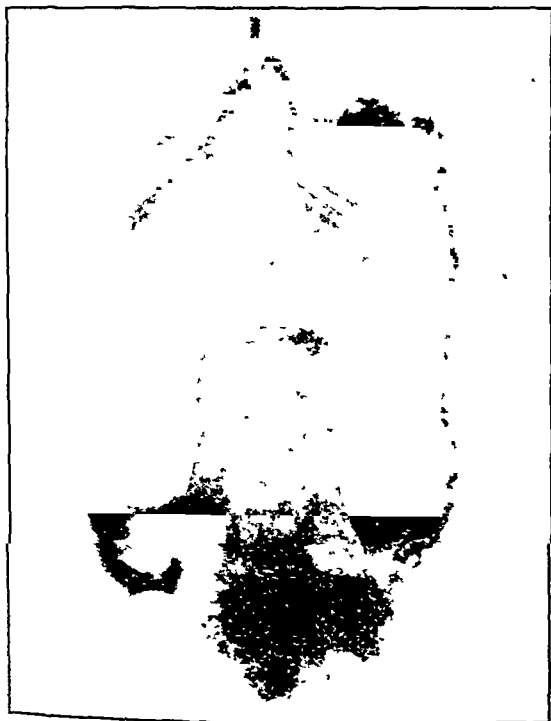


FIGURE 4. Roentgenogram of a Barium Enema in a Patient (Case 5) with Lymphosarcoma of the Ileum.

An ileocolic intussusception was partially reduced by the radiologist, with a residual filling defect in the cecum.

masses. The liver and spleen were not enlarged. The rectum contained concretelike fecal material. No other ab-

8 per cent lymphocytes and 5 per cent monocytes. No immature cells were noted, and the platelets appeared normal.

Cleansing enemas were given and copious fecal masses were evacuated, but there persisted a hard, grapefruit-sized mass in the lower midabdomen that could not be reached on rectal examination. On the 5th day signs of acute intestinal obstruction developed. A barium enema revealed displacement of the sigmoid to the left by a large, soft-tissue mass in the lower abdomen. In addition, there was an intussusception reaching the hepatic flexure; this was partially reduced by the roentgenologist (Fig. 4).

Laparotomy was immediately carried out and revealed a grapefruit-sized, hard, rubbery, yellowish-white tumor. The terminal ileum ran directly through the mass, which was situated 25 cm from the ileocecal junction. The omentum was densely adherent to the anterior surface of the tumor, and the latter extended across to the sigmoid, which it had invaded. Four or five yellow plaque-like tumors measuring 4 to 6 cm. in diameter were present in the proximal ileum, jejunum and root of the mesentery. The terminal 15 to 20 cm. of the ileum was edematous and reddened, suggesting a spontaneously reduced intussusception. The large tumor of the ileum was freed from its attachments to the omentum and sigmoid, and a Mikulicz resection of the terminal ileum bearing the tumor was carried out (Fig. 5).

Postoperatively the patient went steadily downhill, rapidly developing malignant cachexia. Recurrent intestinal obstruction necessitated Miller-Abbott suction and a second laparotomy with lysis of adhesions. One thousand three hundred and fifty r of roentgen-ray therapy was given. During the 4th week lymphoblasts appeared in the blood smears. The spleen became enlarged, and the whole lower abdomen became filled with masses of tumor. There was a terminal leukopenia with diminished platelets and a rise in lymphoblasts to 16 per cent. The patient died on the 39th postoperative day.

The surgically excised tumor of ileum showed on microscopical examination masses of rapidly growing lymphoblasts exhibiting numerous mitoses (Fig. 6). Autopsy showed severe emaciation and purpuric hemorrhages in the skin and viscera, with massive extensions of tumor to the mesenteric and aortic nodes, several loops of the ileum and the sigmoid and bladder. Metastatic nodules were present in the kidneys,



FIGURE 5. Photograph of a Resected Lymphosarcoma of Ileum That Had Extended to the Sigmoid and Root of the Mesentery (Case 5).

normalities were noted. Urinalysis was negative. The red-cell count was 3,800,000 and the hemoglobin 60 per cent. The white-cell count was 11,900, with 87 per cent neutrophils,

diaphragm, liver, lungs, testes and spleen. The bone marrow was heavily infiltrated. Diagnosis: lymphosarcoma, with generalized metastases.

Physical examination on admission showed a pale, thin boy with a hard, smooth, lemon-sized tumor on the posterior rectal wall, extending to the brim of the pelvis. There were no other significant findings. Routine blood and urine examinations were normal. Roentgenograms of the skull, chest and skeletal system showed no evident metastases.

into the lumen, except over a 2-cm. ulcerated area near the center of the mass (Fig. 2). Microscopical examination revealed a tumor consisting of large polygonal cells with abundant purplish cytoplasm and clear vesicular nuclei. Phagocytosis was prominent. Tumor cells were found in the blood vessels and lymphatics and diffusely infiltrated the entire rectal

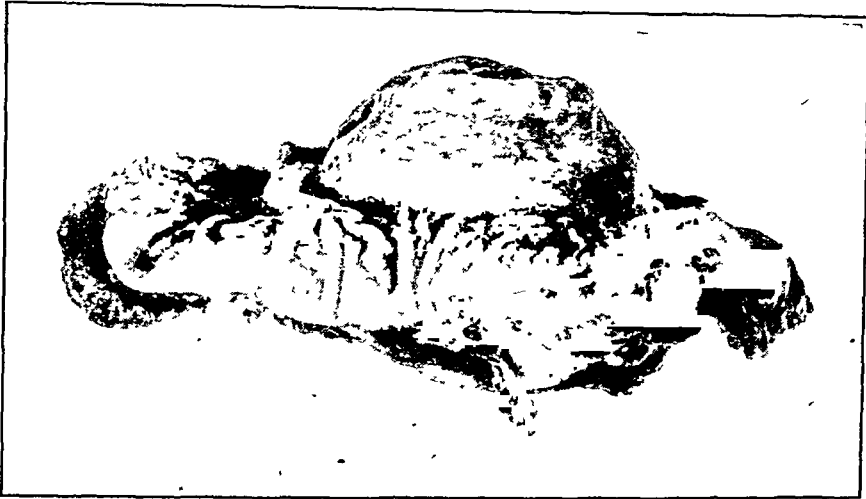


FIGURE 2. Photograph of a Resected Reticulum-Cell Sarcoma of the Rectum (Case 4).

Consequently, a one-stage combined abdominoperineal resection of the rectum and lower sigmoid containing the neoplasm was carried out. The tumor lay in the wall of the rectosigmoid and was removed intact. Several large nodes in the mesosigmoid were excised. Postoperatively, the patient did well except for a troublesome urinary infection. He was given a

wall, but did not extend through the serosa (Fig. 3). Reticulum fibers were demonstrated by Foot's stain. Diagnosis: reticulum-cell sarcoma.

CASE 5. G. H. (CH283174), a 6½-year-old boy, was admitted in May, 1944, with fecal impaction and a story of



FIGURE 3. Photomicrograph of a Reticulum-Cell Sarcoma of the Rectum (Case 4). Note the tumor cells in the lymphatic vessel.

total of 3000 r of roentgen-ray therapy to the abdominal drainage area and was discharged home on the 60th day. He has remained in good health and has shown no evidence of recurrence of tumor.

The excised rectum and lower sigmoid contained a hard, spherical, yellowish intramural tumor measuring 7 by 4.6 by 4 cm. The rectal mucosa covered the tumor, which bulged

progressive constipation following appendectomy at another hospital 4 months before entry. There had been no bowel movement in the 7 days prior to admission, and for 2 days the patient had had crampy epigastric pain. There had been no vomiting, anorexia, weight loss or melena.

Physical examination showed a thin boy with a protuberant, distended abdomen filled with hard, nontender movable

## SHOCK IN ACUTE INFECTIONS

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THE recognition and treatment of shock have received much attention in the last few years, especially since the beginning of the war. Emphasis has been focused largely on the shock that occurs following surgical emergencies, such as injuries, hemorrhage and burns, and little attention has been directed toward shock in the course of acute infections. Since the occurrence of shock in association with infections is not infrequent, it is the purpose of this paper to stress the importance of the recognition of this syndrome and its vigorous treatment in combination with equally vigorous specific treatment of the infection.

Shock, regardless of its cause, is the result of a disparity between the circulating blood volume and the size of the vascular system. This may occur as a result of a loss of fluid from the circulation or an uncompensated increase in the size of the vascular bed. The latter factor is of most significance in the present study, although undoubtedly dehydration does play a part. Clinically this syndrome is manifested in the typical case by apathy, a cold, clammy skin, shallow respirations, a thready, rapid pulse and low blood pressure.<sup>1-3</sup> It has been the intent of recent surgical studies to point out the need for earlier diagnosis and thus earlier treatment of shock in order that the irreversible state toward which this condition tends to progress may be prevented.<sup>1,4</sup> In acute overwhelming infections, however, it is often impossible to anticipate the development of secondary shock, which frequently occurs precipitously. The peripheral vascular dilatation so often seen in acute infections is not to be confused with shock. The former is characterized by a flushed, warm skin, a bounding pulse, digital pulses and murmurs over the great vessels and is due to arteriolar dilatation, which is the customary response of the body to fever.<sup>5</sup>

The recognition of shock of the so-called "secondary type," or what may better be termed "cold shock," during the course of acute infection is not new. The weak heart sounds of a failing circulation in acute febrile illnesses were described in 1831 by Laennec,<sup>6</sup> but were erroneously attributed by him to heart failure. This concept of heart failure persisted in the medical literature, and it remained for Janeway<sup>7</sup> to show that the vascular collapse seen in the course of severe infections was due not to heart failure but to failure of the peripheral circulation with pooling of the blood in the capillaries. In his paper, he stressed vasomotor failure as the cause of death at the height of such infectious diseases as pneumonia, typhoid fever and septic fevers and referred to the experimental work of Romberg, Pässler et al.<sup>8</sup> The latter authors as

early as 1899 had produced vascular collapse in rabbits by the intravenous injections of various bacteria, and had suggested the term "toxic shock" for the apparently similar vascular collapse occurring in acute infections. In 1930, Atchley,<sup>9</sup> in an exceedingly informative paper again brought out the importance of shock in medical conditions and stressed its early recognition and treatment, and in 1934, he and Loeb<sup>10</sup> reported studies along similar lines. The appearance of shock due to hemolytic streptococcus infections of postoperative wounds was emphasized by Stewart.<sup>11</sup> In all of Stewart's cases the state of shock was recognized and specific antishock therapy was instituted. The infection producing the shock, however, was not immediately recognized, and all the patients died in spite of adequate shock therapy in the absence of vigorous antibacterial therapy.

The following cases are typical of the therapeutic problems presented by three serious infections not infrequent in Army medical practice. We do not believe that these cases are comparable to those of Ebert and Stead,<sup>12</sup> whose patients were in the older age group and thus more prone to degenerative changes of the cardiovascular system.

**CASE 1.** A 37-year-old man was admitted to the hospital with a history of cough for several days and chilliness on the day preceding admission. Examination revealed nasal congestion and moderate pharyngeal injection. The white-cell count was 4000, with 58 per cent polymorphonuclear leukocytes and 42 per cent lymphocytes. The urine was free of albumin and sediment. Its specific gravity was 1.020. The oral temperature was 99.4°F. The course was benign until the afternoon of the 3rd hospital day, when the temperature rose to 103°F. At that time the patient's face was flushed and he vomited and had mild diarrhea. The vomiting continued, and at about 7:00 p.m. he developed a typical scarlet-fever rash.

The patient's general condition rapidly deteriorated. At 6:00 a.m. of the 4th day the rectal temperature was 105.4°F., the pulse 140, and the respirations 40 to 50 (Fig. 1). The white-cell count was 11,850, with 80 per cent polymorphonuclear leukocytes. Shortly he lapsed into a state of profound cold shock, the rectal temperature fell to 100°F., the extremities became cold and clammy, the pulse threadlike and barely perceptible and the lips cyanotic. The systolic blood pressure was 58; the diastolic pressure could not be determined. There was marked air hunger, and the patient had severe hiccoughing.

Energetic treatment was promptly begun. One hundred cubic centimeters of pooled human convalescent scarlet-fever serum was administered intravenously. The patient was placed in an oxygen tent, and an infusion of 1000 cubic centimeters of 5 per cent glucose in normal saline solution followed by 1000 cc. of plasma was administered during the first 24 hours. At the outset of the rather sudden collapse, he had been given caffeine. The hematocrit index prior to the giving of the plasma was 56 per cent and blood nonprotein nitrogen was 58 mg. per 100 cc. Intravenous fluids were continued, and the pulse gradually improved in quality and slowed so that it fell below 100 in 48 hours. The respirations returned to normal 24 hours after treatment of the scarlet fever and shock was instituted.

At 7:00 p.m. on the 4th day, the blood pressure began to rise and reached 70/54 at that time. On the following day it

## DISCUSSION

Preoperative recognition of lymphosarcoma of the intestinal tract in childhood offers many difficulties. In adults, bowel lesions of this type are usually confused with carcinoma until histologic examination clarifies the issue. The extraordinary rarity of carcinoma of the bowel in children is of considerable aid in differential diagnosis, and in all probability the practical consideration that a neoplasm of the intestinal tract in an infant or child is

## SUMMARY

Four cases of lymphosarcoma and 1 case of reticulum-cell sarcoma of the bowel treated at the Children's Hospital during the last fifteen years are reported.

The pathologic and clinical aspects are discussed. Radical surgical extirpation followed by roentgen-ray therapy seems to be the most logical treatment.

The mortality in this series was 80 per cent. Two patients developed terminal lymphatic leukemia.

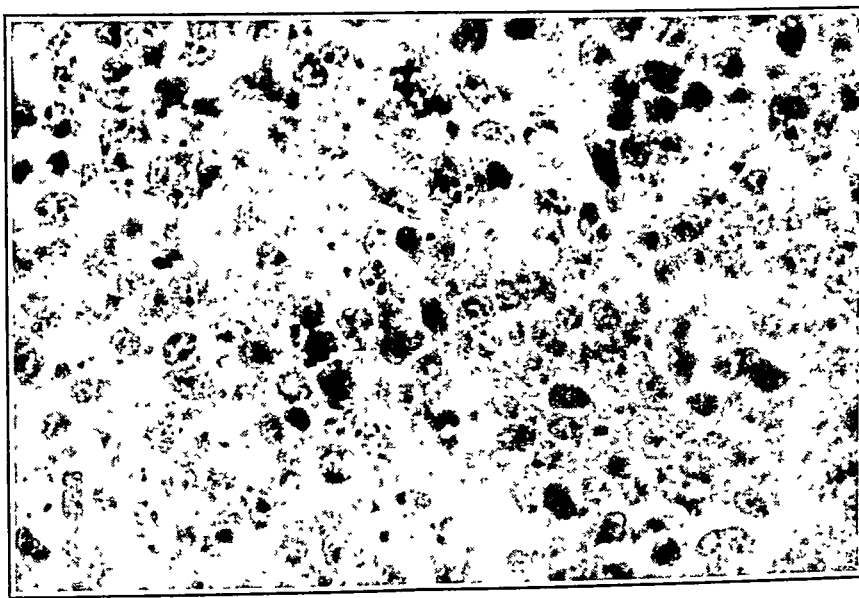


FIGURE 6. Photomicrograph of a Lymphosarcoma of the Ileum (Case 5).  
Note the large lymphoblasts with numerous mitoses.

lymphosarcoma until proved otherwise is justifiable. The frequency of intussusception seems worthy of comment. This occurred in 3 of these 5 patients.

In our opinion a combination of radical surgical extirpation of the involved bowel and mesentery followed by heavy roentgen-ray therapy to the abdominal and mediastinal drainage areas offers the patient the optimal chance of survival, if, indeed, any such chance may be called optimal in this highly fatal disease. The mortality in this series was 80 per cent. The sole surviving patient has had no evidence of recurrence during the fifteen months since the abdominoperineal resection of the rectal tumor.

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was 90/68, and on the 6th day 110/80. Thereafter it remained within normal limits.

From the outset of the patient's acute collapse and for 72 hours thereafter he was anuric, and the blood nonprotein nitrogen rose to 130 mg. per 100 cc. Improvement in the renal function paralleled the rise in blood pressure, and the

commenced, breaking out over the entire trunk, extremities and face and even involving the mucous membranes of the mouth and pharynx. The pulse was imperceptible, and the systolic blood pressure was 65. Respirations were shallow at 40, and the rectal temperature was 101°F. The white-cell count was 24,000, with 95 per cent polymorphonuclear leukocytes. A diagnosis of septicemia with severe secondary shock was made, and blood cultures were taken that later grew Type 2a meningococci. The spinal fluid was clear, and no organisms could be cultured from it.

Antibacterial therapy was immediately instituted and consisted of 5 gm. of sodium sulfadiazine in 100 cc. of sterile water intravenously and 4 gm. of sulfadiazine by mouth, followed by 1 gm. of sulfadiazine orally every 4 hours. Sodium bicarbonate was administered orally — 3 gm. per gram of sulfadiazine. Concomitantly with the institution of chemotherapy, efforts were directed to combat the severe and apparently progressive shock that the patient manifested. Two thousand cc. of 5 per cent glucose in normal saline solution, 1000 cc. of 10 per cent glucose in distilled water and 500 cc. of plasma were administered daily for the first 3 days. In addition, the patient was urged to take water and fruit juices by mouth. Five milligrams of cortate was given intramuscularly every 4 hours, and the foot of the bed was elevated on shock blocks.

On this regimen a blood pressure of 60/40 to 80/50 was maintained for the first 2 days. One hundred and five cubic centimeters of urine was passed the first day. On the second day, however, a total of 1500 cc. of urine was passed, and from then on the urinary output remained satisfactory. The

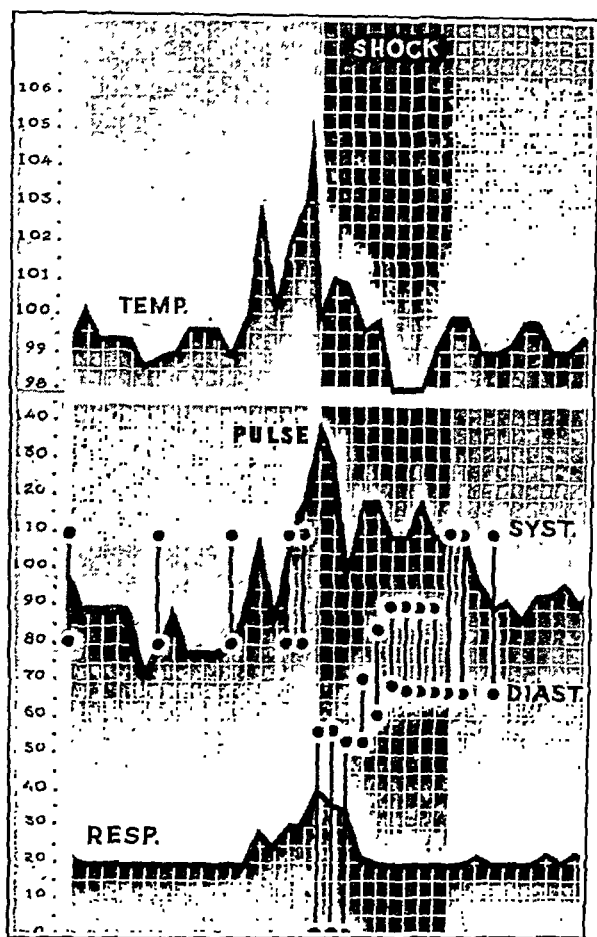


FIGURE 1. Scarlet Fever (Case 1).

In this and the two subsequent figures, each vertical subdivision represents a four-hour period. The temperature recordings were oral, except in the darkly shaded "shock" areas, when they were rectal.

blood nonprotein nitrogen gradually dropped, becoming normal 6 days later. There was never any evidence of cardiac failure, and the patient was eventually discharged to duty.

**CASE 2.** A 37-year-old officer was admitted to the hospital complaining of generalized malaise, chilly sensations and a mildly sore throat. He had felt perfectly well until 2 hours prior to coming to the hospital, at which time he commenced to feel chilly and thought he was coming down with a "cold."

Physical examination showed an injected throat of moderate severity but was otherwise negative. The temperature was 102°F., the pulse 105, and the respirations 19. The white-cell count was 13,600, with 67 per cent polymorphonuclear leukocytes and 33 per cent lymphocytes. The urine was negative. A tentative diagnosis of pharyngitis was made and the patient was admitted to a respiratory ward.

Early the next day — 9 hours after admission — he experienced a severe chill and the temperature rose to 105°F. (Fig. 2). Physical examination was still essentially negative, although the patient's general appearance was quite toxic. Six hours later a profuse, blotchy, hemorrhagic skin rash

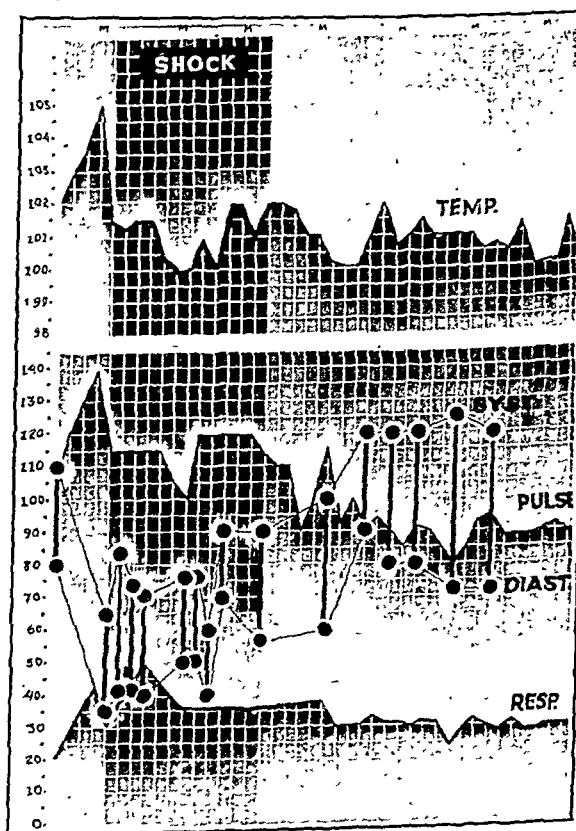


FIGURE 2. Meningococcemia (Case 2).

blood pressure rose to 100/60 on the afternoon of the 3rd day and over the next 3 days gradually returned to a normal level (120/80). Intravenous fluids were abandoned after the 3rd day. Chemotherapy was stopped on the 12th day, and convalescence was uneventful.

CASE 3. A 25-year-old soldier was admitted to the hospital because of a cough and moderate pain in the right chest of 4 days' duration. His previous health had been excellent. On admission he was moderately ill.

Physical examination revealed rales over the right lower lobe, and an x-ray film taken the day of admission showed an

was secondary to the acute infection. He was given 2000 cc. of 5 per cent glucose in normal saline solution and 500 cc. of plasma over the next 12 hours. Simultaneously with the above measures, he was placed in an oxygen tent and started on sulfadiazine therapy. Five grams of sodium sulfadiazine was given intravenously, followed by 1 gm. of sulfadiazine orally every 4 hours. Sodium bicarbonate was given orally, 3 gm. per gram of sulfadiazine.

The blood pressure gradually rose to 120/70 over the next 24 hours, and with its return to normal all signs of shock disappeared and the urinary output improved. Because the patient continued to run a febrile course, however, he was given 200,000 units of Type 3 antipneumococcus serum in addition to the sulfadiazine. The spiking fever persisted, and on the 8th day signs of fluid developed in the right chest. A right-sided thoracentesis revealed purulent fluid containing pneumococci. On the 20th day closed-tube drainage of the right chest was instituted, and from then on convalescence was uneventful.

Figures 1, 2 and 3, which record the temperature, pulse, respirations and blood pressure determined at four-hour intervals in each case, emphasize several points of similarity that are readily noted graphically and that may warn clinicians of impending events. There was an abrupt rise in temperature to a high level shortly preceding the overwhelming spread of the infection. This was followed by an equally abrupt fall in temperature, although the pulse and respirations did not correspondingly drop. Oliguria was present during the period of hypotension. Each patient had been examined prior to the onset of shock and clinically presented evidence of an essentially negative cardiovascular system and appeared to be in good fluid balance.

The mechanism producing the shock in all 3 cases is probably due to the sudden invasion of the vascular system by bacteria or bacterial toxins or both that paralyzes and dilates the capillary bed. A pooling of blood occurs in the dilated capillaries, with a concomitant reduction in the venous return to the heart and in the cardiac output. Romberg et al.<sup>8</sup> demonstrated in 1899 that the injection of bacteria and bacterial products intravenously could produce vascular collapse, and other investigators<sup>10,13</sup> have confirmed their findings.

The first case presented in this study was one of severely toxic scarlet fever. Presumably in this type of case one is dealing with a true bacterial exotoxin that is absorbed into the blood stream. By the intravenous administration of pooled convalescent scarlet-fever serum the temperature and some of the toxic manifestations were controlled. However, the tone of the vascular system did not return until the fourth day, and during that time intravenous fluid and plasma were necessary to maintain the blood pressure at a critical level. The disparity between the circulating blood volume and the size of the vascular bed was further aggravated by the loss of fluid through vomiting and diarrhea.

The second case was one of a fulminating meningococcemia, with a massive invasion of the blood stream by bacteria and bacterial products. As is

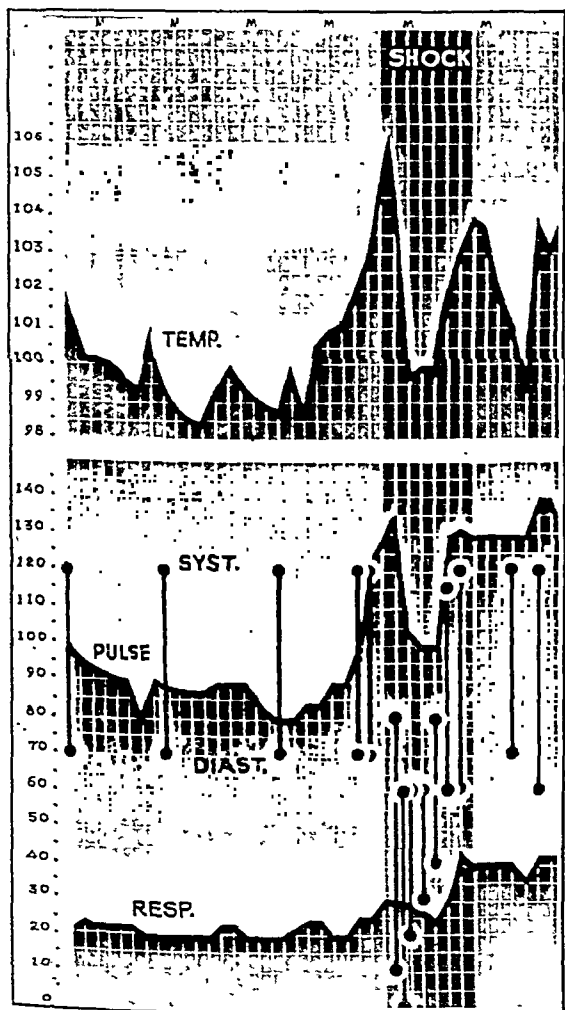


FIGURE 3. *Pneumococcus (Type 3) Pneumonia (Case 3).*

infiltration in the same area. The temperature was 102°F and the white-cell count 10,400, with 69 per cent polymorphonuclear leukocytes. The urine was normal. A diagnosis of primary atypical pneumonia was made, and the patient received symptomatic therapy.

During the first 4 hospital days his course was uneventful and he appeared to be recovering. On the 5th day the rectal temperature rose to 106.2°F. (Fig. 3) in 4 hours. The respirations became labored. The blood pressure dropped precipitously from 120/70 to 70/0 and later to 60/0, and shortly thereafter the rectal temperature decreased to 100°F. The skin was cold, and the pulse was imperceptible. The patient was extremely restless, and there was cyanosis of all the extremities.

Examination of the chest at that time revealed signs of frank consolidation at the right base, although the white-cell count was still only 12,000, with 74 per cent polymorphonuclear leukocytes. The sputum contained Type 3 pneumococci. Blood cultures were negative. It was believed that the patient had developed a severe bacterial pneumonia superimposed on the original infection and that the state of profound shock

well known, many of these patients die in severe shock before the infection can be controlled by chemotherapy. In this case again, it was possible by the use of intravenous fluid and plasma to maintain the circulating blood volume and blood pressure at a critical level until the infection could be controlled by sulfadiazine.

In the third case, one of Type 3 pneumococcus pneumonia, although blood cultures failed to demonstrate a septicemia it was thought that the severe state of peripheral vascular collapse was due to an invasion of the blood stream both by bacteria and by bacterial products. Here again, while the infection was being treated energetically with sulfadiazine and Type 3 anti-serum, the circulating blood volume was maintained by intravenous plasma and fluids.

The institution of specific measures to combat the infection is of primary importance, since they are directed at the cause of the shock state. It is our contention, however, that death in the early stages of acute fulminating infections may occur as a result of secondary shock; furthermore, if vigorous anti-shock therapy directed to maintain an adequate circulating blood volume is resorted to, as in the cases cited above, many patients may be maintained until specific serum or chemotherapy or both have been able to control the infection.

It is considered advisable to give warning that overly enthusiastic use of procedures designated to restore inadequate circulating blood volume in patients with certain types of acute pneumonia, particularly interstitial pneumonia, so frequently seen in young children, may result in an increase in exudation in the lungs and harm to the patient.

## SUMMARY

Shock during the course of acute infection is discussed, and its importance as a preventable cause of death is stressed.

In the treatment of shock in acute infections, attention is called to the need for maintaining an adequate circulating blood volume by the use of intravenous plasma and fluids while the infection is being vigorously treated by appropriate chemotherapy or serotherapy. The use of oxygen in the face of anoxemia and other supportive measures are not to be neglected.

Three case reports that illustrate acute infections not infrequently seen in medical practice and that presented serious states of shock are given in detail, with their treatment.

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## MEDICAL PROGRESS

## OPHTHALMOLOGY

EDWIN B. DUNPHY, M.D.\*

BOSTON

THE following ophthalmologic subjects have been selected as being of general interest. Some of them are not new, but because of recently revived interest in them, they were thought to deserve review.

## RELATION OF GERMAN MEASLES TO CONGENITAL CATARACTS

One of the most interesting recent developments in the field of ophthalmology has been the recognition of the fact that congenital cataracts can be caused by German measles occurring in the mother early in pregnancy. Gregg,<sup>1</sup> of Sydney, was the first to point out this relation, and in 1941 he reported a series of cases to the Ophthalmological Society of Australia. He stated that in the summer of 1940 there had been an epidemic of unusually severe rubella in southeastern Australia. The following year there occurred a great increase in the incidence of congenital cataracts among the newborn of Sydney and other neighboring cities. Gregg reported 78 cases of cataracts, 20 of which were seen by him and the remaining 58 by colleagues and reported to him. In all but 10 cases, a history of rubella during early pregnancy was obtained. The cataracts were bilateral in 62 cases and unilateral in 16. Microphthalmia was present in 10 of the unilateral cases.

According to Gregg, these cataracts were of a special type, being dense white with all layers of the lens involved. Most of the babies were small and ill nourished and presented definite feeding problems. Forty-four of them had congenital heart disease. Fifteen deaths were recorded. Autopsy in 3 cases revealed patency of the ductus arteriosus.

An interesting feature was the reported intolerance to atropine exhibited by all these infants. When 1 or 2 drops of a 0.5 per cent solution of this drug were used to dilate the pupils, considerable constitutional disturbance took place, consisting of flushing of the skin, pyrexia and disturbed digestion.

Gregg believed that there was more than a casual relation between the attack of rubella and the occurrence of the congenital cataracts. In 35 cases in which accurate records were available, the affected baby was the first child in 26 cases, the second child in 3, and the third, fourth, fifth, sixth, eighth and tenth child in the remaining. Other children in the families showed no signs of cataracts, nor did the parents.

Gregg raised the question whether the causative factor was really German measles because of the severe epidemic of sore throat that was sweeping the country concurrently with the rubella, most of the mothers having had tonsillitis at the time of their illness. He suggested that the rash diagnosed as German measles might have been a toxic erythema accompanying a streptococcal throat infection.

Naturally this report stimulated great interest throughout Australia, and under the direction of the National Health and Medical Research Council a group was appointed to determine the following points: whether the disease of the mothers was rubella or some illness simulating it, the period of pregnancy in which the disease produced congenital defects, the full extent of these defects and whether these defects could have been produced by other infectious diseases during pregnancy. This extensive investigation was conducted by Swan, Tostevin, More, Mayo and Black.<sup>2</sup> All the physicians in certain sections were circularized, and all pregnant women with exanthematous diseases were registered. All new cases of congenital cataracts in infants were investigated, and the history of each mother was carefully gone over for evidence of prenatal illness. The results of this study were published in 1943 and showed that of 61 infants examined, 36 had congenital defects. Forty-nine of the mothers had had rubella during pregnancy, 9 had had morbilli and 2 mumps; 4 denied knowledge of any disease. Of the 49 mothers with rubella, 31 gave birth to infants with congenital defects. Of these, 13 had cataracts, in 10 of whom they were bilateral, 1 had buphthalmos, 7 were deaf mutes, and 17 had cardiac anomalies. Some degree of microcephaly was apparent in all. All but 2 of the mothers of the infants with congenital defects had contracted rubella during the first three months of pregnancy.

It was the conclusion of the investigators that there was no valid evidence that the epidemic of 1940 was other than rubella and that the predominating organism in the concurrent epidemic of sore throat was *Haemophilus influenzae*. Furthermore, they stated that subsequently, when there was no epidemic of sore throat, congenital cataracts were found in the offspring of mothers who had had German measles.

In a subsequent communication, the same authors<sup>3</sup> reported 12 additional cases of rubella occurring during early pregnancy, eleven of the infants showed congenital defects. These included 2 cases of cataracts, 5 of deaf mutism and 4 of heart disease,

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well known, many of these patients die in severe shock before the infection can be controlled by chemotherapy. In this case again, it was possible by the use of intravenous fluid and plasma to maintain the circulating blood volume and blood pressure at a critical level until the infection could be controlled by sulfadiazine.

In the third case, one of Type 3 pneumococcus pneumonia, although blood cultures failed to demonstrate a septicemia it was thought that the severe state of peripheral vascular collapse was due to an invasion of the blood stream both by bacteria and by bacterial products. Here again, while the infection was being treated energetically with sulfadiazine and Type 3 anti-serum, the circulating blood volume was maintained by intravenous plasma and fluids.

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Post<sup>17</sup> has collected the records of 57 cases of myopia in which the vision was definitely improved by one or another type of exercise. One of the most remarkable of these cases was that of a twenty-four-year-old man whose vision had become progressively worse through the years, it being 20/200 in each eye corrected to 20/20 with about -2.00 spheres and small cylinders. These tests had been made under a homatropine cycloplegia. Being rejected for military service, he took so-called "muscle exercises" for twenty-four lesson periods, at the end of which he was able to see 20/20 with each eye without glasses. Homatropine refraction then showed the same error as he had had before taking the exercises! In this case, care had been taken to prevent memorizing the test letters. The same ophthalmologist examined the patient on both occasions. Since his refractive error under the cycloplegia had not changed, his great improvement must have been due to learning how to use his visual powers to the utmost advantage by practice and repetition.

According to Lancaster, "seeing is only partly a matter of the image on the retina but is, in still larger part, a matter of cerebral synthesis in which memories play a principal role. By repetition one builds up a substratum of memories very useful for the interpretation of sensations and facilitates the syntheses which are the major part of seeing." Experience has shown that, although some patients are improved by these methods, the improvement is usually not lasting. Many patients state that they did not have time to keep up their exercises and eventually went back to wearing glasses. The dangers of the unsupervised use of these exercises in cases of detached retina and glaucoma have been pointed out by Duke-Elder.<sup>18</sup>

Men rejected for military service because of color blindness often apply for treatment to cure their defect. A number of optometrists have claimed that they are able to help these persons. The treatment consists in fixation of colored lights, the sorting of colored beads and the use of filters in viewing the test plates. By constant repetition the patients learn to interpret their sensations more efficiently, and undoubtedly a number of them have been able to pass the test. Subsequent reports from the Army and Navy<sup>19</sup> indicate, however, that the improvement in such cases has not lasted, patients later on having fallen down badly in critical situations that required accurate color perception.

According to Bridgman and Hofstetter,<sup>20</sup> two optometrists at Ohio State University, the alleged improvement in color vision after this type of training is due to learning made possible after repeated testing. They illustrate this by the report of a color-blind subject who at his first examination scored only 15 out of 46 plates. He was merely told each time that he was wrong but was not told the correct answer. On the second, third, and fourth test-

ings, his scores were 27, 35 and 43 correct. These authors concluded that the color-filter treatment is not only ineffective in curing color blindness but is, in fact, dangerous, since it leads persons into the acceptance of responsibilities that they will be unable to fulfill.

It must be kept in mind that there are various degrees of color blindness and that in mild cases repeated testing leads to proficiency in correctly naming the test plates. When the scene is changed, however, such persons are still found to be "color weak." This is borne out by some recent unpublished work by Gallagher<sup>21</sup> and his associates. Forty-five students were selected as being color weak from their responses to the American Optical Company pseudoisochromatic test plates<sup>22</sup> and were given training on these plates until all could pass the test perfectly. They were then tested on the Ishihara plates,<sup>23</sup> which are quite similar, but only 6 of them made perfect responses on this test, which was unfamiliar to them. Several months later, 15 of them were retested on the American Optical Company plates and a sharp decrease in their ability again to name these plates correctly was noted. Even when these 45 students were at the peak of their proficiency in passing the American Optical Company test, they were unable to pass the color-desaturation test. In this test various saturations of red and green light are thrown on a screen in random order and the subject is asked to say whether the color is red or green. Gallagher and his associates conclude that there is no evidence that color training improves the ability of a color-weak subject to discriminate between colors except in the situation in which the training is given.

#### EFFECT OF FLUORESCENT LIGHTING ON EYES

The fluorescent lamp has been an important development in electric lighting. Since its introduction some years ago, however, there have been many complaints that it is fatiguing to the eyes. Physicians are often asked by their patients whether it is actually harmful. It may be helpful, therefore, to review the evidence on this question.

The fluorescent lamp is a mercury-vapor lamp giving off chiefly ultraviolet radiations within a tube. The inside of the tube is coated with certain substances that fluoresce under this radiation. No ultraviolet light reaches the eye, as is generally believed by the laity. The lamp has the advantage of producing three times as much light per watt as the regular incandescent lamps. Another advantage is the relatively low degree of radiant heat given off when high levels of illumination are used, daylight fluorescent lamps giving forth only one quarter as much heat as an incandescent lamp of equivalent light output.<sup>24</sup> Furthermore, the comparative low brightness per square inch of glass surface and the long form of the tubes make it possible for the

If these two series are combined, it is seen that of 61 mothers who had rubella during pregnancy, 42 gave birth to children with congenital defects and of these 15 had cataracts. In analyzing the data, the investigators concluded that if a woman contracts German measles during the first two months of pregnancy, the chances of a congenitally defective infant are practically certain. If the disease occurs during the third month, about half the infants will be affected.

During the past year several American reports have corroborated Gregg's original findings. Thus, Reese<sup>4</sup> reports 3 cases of dense white cataracts and congenital heart defects in infants whose mothers had been treated for rubella during the first month of pregnancy. Rones<sup>5</sup> reports 3 maternal cases of rubella and 1 of morbilli. In 2 of these cases the exanthema had occurred in the second month of pregnancy and the infants were born with bilateral cataracts; 1 of them had congenital heart disease. In the other 2 cases the disturbance took place in the third month and the infants were born with congenital glaucoma.

Erickson<sup>6</sup> reports 9 cases of congenital cataracts in infants born of mothers who had had rubella during the first two and a half months of pregnancy. All but 2 of these showed heart defects in addition to the cataracts.

It is known that important developmental changes take place in ocular and cardiac tissues of the embryo during the first three months of pregnancy.<sup>7</sup> It is also known that embryonic tissues are especially susceptible to virus infections. Goodpasture<sup>8</sup> has pointed out the greater susceptibility of chick embryo, as compared with the hen, to a wide variety of infections inoculated in the chorioallantoic membrane. It is not improbable that the human embryo possesses the same increased susceptibility, so that infections such as German measles, which cause only slight or no damage to adult tissues, result in profound changes to embryonic cells.

With formation of the placenta at the end of the third month of pregnancy, there is apparently a reduction in the penetrability of the barrier between mother and fetus. This may in part explain the decreased incidence of congenital defects when the infections occur in the later months of pregnancy.

Little is known concerning the exact mechanism of cataract formation. Swan and his co-workers<sup>2</sup> suggest interference with the nutrition of the lens by action of the agent on the hyaloid artery. It seems more probable, however, that the lens is directly affected.

This whole subject brings up the question of whether abortion is justified if a woman contracts rubella during the first three months of pregnancy. Certainly it is desirable that girls be exposed to this disease before marriageable age. There are, of course, practical difficulties in this procedure.

## EYE EXERCISES FOR IMPROVING VISION

The question of eye exercises to improve visual acuity is one that crops up perennially and has for years been the subject of bitter debate. The Bates method,<sup>9</sup> originally brought forth in 1920, has recently been repopularized by Huxley's<sup>10</sup> book *The Art of Seeing*.

Bates, a New York physician, claimed that accommodation was due not to an increase in the convexity of the lens, as is generally believed, but to a change in the shape of the eyeball brought about by the action of the superior and inferior oblique muscles. He believed that all refractive errors were due to the unbalanced pull of these muscles. The animal experiments on which he based this theory were open to certain criticisms. Also, his claim that the cure of all refractive errors lies in so-called "dynamic relaxation," which can be brought about by certain exercises, was not accepted by the medical profession. The method was employed by many cultists, and after enjoying several years of popularity with the public gradually fell into disrepute, only to have a renaissance in recent years when men were being rejected for military service because of eye defects. Although the majority of orthodox ophthalmologists<sup>11-15</sup> decry such antics as "palming, swinging the eyes, sunning, thinking of black velvet and so forth" as pure nonsense, one must nevertheless admit that there are a certain number of people who, by these methods, do achieve improvement in their visual acuity without the aid of glasses. To the simple neurotic such a system may be expected to give aid and comfort. It is also understandable that it might benefit borderline cases of myopia, since many patients are not really myopic but, owing to excessive accommodation, have brought the focal point of the fixated object anterior to the retina, thus producing an artificial myopia. Learning to relax their accommodation, by whatever means employed, results in their being able to see normally without glasses. Lancaster,<sup>16</sup> who has approached the subject with an unbiased mind, illustrates this point with the story of a young man who came to him asking whether there was any chance of his passing the 20/20 visual test. His vision with his weak myopic lenses was 20/15 but without them was only 20/30. He was given +1.00 spheres to wear constantly for three days. He then read 20/15 without glasses. This man was not a true myope; he had simply learned to relax his accommodation by wearing convex lenses for a while. The same results could probably have been obtained by the Bates exercises.

Even in true myopes, going without glasses for a few days and learning to relax often results in some visual improvement on the test chart. It is not that the refraction has changed essentially, but that the patient has learned to interpret blurred objects more or less correctly through practice. This point has been emphasized by Lancaster.

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor\**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 31231

#### PRESENTATION OF CASE

A sixty-three-year-old business man was admitted to the hospital because of fever, dyspnea, inability to urinate and exacerbation of a chronic scrotal infection.

For several years he had had nocturia, frequency and hesitancy. These symptoms progressed, and two years before admission he had a transurethral prostatic resection in a community hospital. On the tenth postoperative day he developed a right epididymitis, which progressed to abscess formation and necessitated a right epididymo-orchectomy. Since that time he had had a draining sinus at the upper angle of the wound. The discharge was offensive and the sinus refractory to local treatment. The patient continued to work despite moderate frequency, a draining sinus and occasional bouts of left scrotal pain and swelling. Seven months before admission he experienced some nausea and abdominal discomfort. He went to another hospital where he was found to have anemia, with a red-cell count of approximately 1,000,000; the spleen was enlarged, extending to the level of the umbilicus. For several months he was treated for anemia. Six weeks before admission he was given three x-ray treatments to the spleen, which allegedly caused some decrease in size and was followed by a rise of the red-cell count. His appetite improved, and he gained weight. Since the operation two years before entry he had been taking 0.1 gm. of digitalis daily. Ten days before admission he experienced malaise and dyspnea and felt vaguely ill. A physician advised bed rest. Shortly after this the patient found that he could not urinate. After several catheterizations he developed pain in and swelling of the left scrotum. The temperature rose to 104°F., and after nine days on sulfadiazine therapy (6 gm. a day, with sodium bicarbonate) he became oliguric and was brought to the hospital. The dyspnea and moderately severe orthopnea, requiring two or three pillows, had continued. A cough that had been present and nonproductive for several years had, during the past few weeks, become productive of yellow, tenacious sputum, especially pronounced on change of position. He

\*On leave of absence.

had had no chest pain, palpitation or swelling of the ankles.

Physical examination revealed a well-developed, well-nourished man with dry, hot and flushed skin. The throat was dry and red. The neck veins were distended and distinctly pulsating. The chest was emphysematous and had limited motion. There were rales in both bases posteriorly and in the axillary region. The diaphragm was low on both sides and showed limited motion. The heart was enlarged to just beyond the left midclavicular line. The sounds were distant. An inconstant apical gallop rhythm developed and persisted. No murmur or thrill was noted. The aortic second sound was greater than the pulmonic. The abdomen was flaccid; the liver was nontender and extended two fingerbreadths below the right costal margin. The spleen extended five or six fingerbreadths below the left costal margin and almost to the midline. There was distinct bilateral costovertebral tenderness, but that on the right side disappeared in a day. There was no fluid, and no other masses were felt. The right scrotum was empty and retracted. There was a small draining sinus at the upper angle of the orchectomy scar. The left testis was tender, and the left epididymis was enlarged, tender and hard, with an overlying warm, red skin. A slight purulent discharge came from the urethra. The penis was normal. Rectal examination revealed little prostatic tissue and no hemorrhoids. There were varicose veins of the legs and mild pitting edema of the lower extremities, sacrum and back. The legs were symmetrical, and the pulsations of the dorsalis pedis arteries were good.

The temperature was 104°F., the pulse 120, and the respirations 50. The blood pressure was 110 systolic, 60 diastolic.

Examination of the blood showed a red-cell count of 2,900,000, with 9.7 gm. of hemoglobin. The red cells showed quite marked anisocytosis and poikilocytosis. The white-cell count was 6400, with 89 per cent neutrophils; there were 2 per cent band forms and 1 per cent myeloblasts. A voided urine specimen was cloudy, amber and acid in reaction. The specific gravity was 1.006. There was a ++ test for albumin, and the sediment contained 3 to 5 granular casts per high-power field, as well as numerous white cells and crystals resembling sulfadiazine; no red cells were seen. The sulfadiazine level of the blood was 2.9 mg. per 100 cc. The serum nonprotein nitrogen was 85 mg. per 100 cc., and the protein 5.8 gm. The albumin-globulin ratio was 1.2. The carbon dioxide and chloride were normal. A smear of the discharge from the scrotal sinus showed no tubercle bacilli, but the culture yielded a moderate number of colonies of *Staphylococcus albus* and a few of a beta-hemolytic streptococcus. The urine culture showed moderate growth of a beta-hemolytic streptococcus and a few colonies of an alpha-hemolytic streptococcus. A Congo red



fixtures to be hung at low levels with an even distribution of light.

Fluorescent lamps operate on alternating current, usually 60 cycles per second. With each change in the direction of the current there is a slight pause during which no current is flowing. This pause is almost infinitesimal, but during it the lamp becomes less bright. Under most circumstances this makes no difference. If, however, the eye is moving rapidly over a wide area, a series of successive images fall on different points of the retina and a series of separate sensations are observed, since each one persists after the next one begins. The same effect can be obtained if the eye is stationary but the object moves rapidly across the field. This flicker may give rise to disagreeable sensations under the above-mentioned conditions, but if only a small stationary area is being viewed, the successive images fall on the same position of the retina and a continuous or fused picture is produced.<sup>25</sup> This stroboscopic or flicker effect can be eliminated by combining tubes in pairs so that the maximum output of one coincides with the minimum output of the other. Indeed, most modern installations are of this type.

The whole question of fatigability under fluorescent light has been investigated by Luckiesh and Moss.<sup>26</sup> They base their conclusions on the results obtained by comparing visual performance under fluorescent light with equivalent illumination from tungsten-filament lamps. After testing a number of subjects they found no difference in visual acuity when either of these two types of illumination was used. The fluctuation in the light output of a daylight fluorescent lamp did not cause ocular fatigue as measured by the rate of blinking<sup>27</sup> during reading. This is not surprising since the flicker of the fluorescent lamp is well above the critical flicker frequency of the human eye and should not be bothersome if the eyes are fixed on a small area. The fixational pauses<sup>28</sup> that occur during reading were electrically recorded and were not found to be prolonged under fluorescent light.

From the above experiments Luckiesh and Moss concluded that there is no basis for the oft-heard criticism that fluorescent light fatigues the eyes. Although the criteria they used may be open to some criticism as not truly determining ocular fatigue, nevertheless no one has been able to bring

forth any valid evidence that fluorescent light in ordinary office use is either harmful or tiring. If care is taken in installing the fixtures to minimize glare and to provide an adequate and even distribution of light, this type of illumination should be just as satisfactory as any other type now in use.<sup>29, 30</sup>

243 Charles Street

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DR. WILLIAM DAMESHEK: When I first saw him the problem was not so much the urinary one that had been in the background but rather the enlarged spleen and anemia. The anemia was of the macrocytic variety, associated with a slightly elevated white-cell count and the presence in the peripheral blood of myelocytes and nucleated red cells. These findings in association with a large spleen make one think of myeloid metaplasia of the spleen, with a faulty liberation of myelocytes and nucleated red cells into the peripheral blood. I like to consider that myeloid metaplasia is not "agnogenic" or "idiopathic" as some observers believe but that it is secondary to some sort of more fundamental disorder of the bone marrow, which is often sclerotic, such as the condition reported by Dr. Chapman<sup>2</sup> some years ago.

X-ray studies of the bones, which were not done here apparently because the patient was too ill, showed the typical picture of osteosclerotic anemia, with irregular areas of osteoporosis and increased density of the pelvic bones and the femurs. Since a sternal puncture failed to bring up enough marrow material for diagnosis, we then did a sternal trephine bone-marrow biopsy, which showed sclerosis of the bone and bone marrow, but in addition hyperplasia of the white-cell elements, interpreted by a pathologist as leukemia. I did not think that this diagnosis was warranted and was inclined to consider the case as one of osteosclerotic anemia with myeloid metaplasia of the spleen. Later, because the patient was going downhill, we tried the effect of a few x-ray treatments over the spleen. The spleen actually (not "allegedly") went down in size and the patient's red-cell count went up. Theoretically, this should not occur in myeloid metaplasia of the spleen. In the background was the chronic urinary infection, which at the time I studied the patient was minimal. Regarding the matter of amyloid disease, I must admit I gave it no consideration.

DR. WYMAN RICHARDSON: I saw this patient and thought that the blood picture suggested pernicious anemia, complicated by a uremic state, although there was also some immaturity of the cells seen in the blood film. I thought that it might be the result of the complicating uremia. I also suggested that he be given liver extract, on the bare chance that he might respond. This was tried, but he had no response.

#### CLINICAL DIAGNOSES

Pernicious anemia?  
Chronic sepsis.  
Uremia.

#### DR. CHAPMAN'S DIAGNOSES

Chronic bacterial sepsis (scrotum and kidneys).  
Amyloidosis of kidney and spleen.

#### ANATOMICAL DIAGNOSES

Splenitis, acute and chronic, with marked splenomegaly.

Epididymitis and orchitis, acute and chronic.

Pyelonephritis, acute and chronic.

Pulmonary emphysema and congestion.

Cardiac dilatation.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this man showed an enormous, moderately firm spleen; it weighed slightly over 1000 gm. In gross we obviously thought of myelogenous leukemia. In fact there were two small infarcts, which one often sees in myelogenous leukemia. The vertebral and sternal bone marrow on gross examination was red, and the marrow in the tibia and femur, which ordinarily is fatty, was pink, indicating hematopoietic hyperplasia. We were not impressed in the gross with the sclerotic character of the bone marrow.

The scrotum still contained a sinus tract, and there was an acute and chronic epididymitis. The epididymis was filled with pus, and the process had extended into the testis. Both kidneys were pale and slightly enlarged, the combined weight being 400 gm. Microscopically they showed an extreme pyelonephritis that undoubtedly was secondary to the scrotal abscesses, the orchitis and the epididymitis. The ureters were not distended but were moderately injected. There was no evidence of amyloid in the kidney or the spleen.

Microscopical examination of the spleen showed a picture that, had one not known about the history of the case, one would have called subacute bacterial endocarditis. There was edema, and widening of the Billroth cords. In the sinuses and throughout the pulp were plasma cells, lymphocytes, hemosiderin-laden phagocytes and polymorphonuclear cells. The appearance was that of long-standing chronic infection. Certainly it could not be called leukemia. That was borne out by the microscopical appearance of the bone marrow, which showed many mature polymorphonuclear and plasma cells, as well as cells of the red-cell series. There was some fibrosis, but this was slight and merely a secondary manifestation of long-standing hyperplasia of the bone marrow. I do not believe that one can call it an osteosclerotic type of anemia. It is the largest spleen that we have seen in chronic sepsis.

The only additional finding that we would have liked to demonstrate in this case is a bacterial endocarditis, but there was none. The lungs were emphysematous and congested, but we found nothing to explain the recent productive cough. The heart was dilated but not hypertrophied.

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test showed 76 per cent of the dye remaining in the blood in one hour. The Hinton test was negative.

X-ray examination of the chest showed diffusely increased vascular markings throughout both lung fields, normal hilar shadows and a smooth diaphragm, with no evidence of fluid in the costophrenic sinus. The respiratory rate was rapid, and the diaphragmatic excursion quite limited. The heart was not grossly enlarged, and the cardiothoracic ratio was 13.9:31 cm. The aorta was somewhat tortuous, with some calcification of the arch. One electrocardiogram on the third day showed auricular fibrillation with almost ventricular rhythm at the rate of 90; there was slight left-axis deviation, with sagging ST<sub>1</sub> and ST<sub>2</sub> and low upright T<sub>1</sub> and T<sub>2</sub>.

No sulfadiazine or salt was given, and the patient was fully digitalized at once. The oral fluid intake was about 2500 cc., and the output about 1750 cc., with a slight parallel rise in these values during the first week. By lysis, the temperature became normal on the fourth day, and the pulse and respiratory curves followed. These remained normal for three days and then began to rise again. The non-protein nitrogen rose to 135 mg. per 100 cc., and two days later, on the eighth hospital day, the patient expired.

#### DIFFERENTIAL DIAGNOSIS

DR. EARLE M. CHAPMAN: It seems evident that this man suffered from chronic bacterial infection, especially of the scrotum, from which area *Staph. albus* and beta-hemolytic streptococci were cultured. The urine was likewise contaminated.

The chronic nonproductive cough that he had had for years became productive of purulent sputum on change of position during his final illness, and then rales were discovered at the lung bases. These facts justify a clinical suspicion of bronchiectasis. Unfortunately the x-ray studies do not help us to establish such a diagnosis.

With this background of chronic sepsis we are next faced with explaining a man's death in renal failure — a rather unusual form of renal failure that was further complicated by the use of two potent and often toxic drugs — digitalis and sulfadiazine.

There seems little question that 54 gm. of sulfadiazine in nine days is excessive, and the cessation of urine flow toward the end of his illness favors a specific type of damage to the kidney. On hospital entry, however, only 2.9 mg. of the drug was found in the blood stream, and no red cells in the urine. These two facts do not support my first suspicion that his kidneys might have shown the granulomatous changes of sulfadiazine intoxication.

As for the digitalis, a person who has taken 0.1 gm. daily for two years, and has nausea and abdominal discomfort seven months before entry, and is then given more of the drug on hospital entry is

apt to become sick. The electrocardiographic changes, especially the sagging of the ST segments, are probable digitalis effects. How can the pathologist help us at autopsy in determining whether or not a person has been toxic from digitalis? I raised this question at the autopsy table recently and received little help.

The next thing to discuss is this man's death in renal failure. What type of kidneys should we expect to find? I am going to commit myself now to that unusual form called the "contracted amyloid kidney" — the kidney that in gross often has the appearance of a chronic glomerulonephritis. With this background of sepsis, allegedly nontuberculous, there might have been the condition favoring the release of protein complexes, with amyloid degeneration in the walls of the blood vessels in the kidneys and spleen.

I now wish to call your attention to the clinical features of renal amyloidosis in this man's record. The patient always had polyuria, — not influenced by transurethral resection, — and even toward the end he excreted a urine of low gravity and with the surprising daily volume of 1750 cc. He also had an anemia, chronic and resistant to treatment and yet not disabling; next, a normal-sized heart and a normal blood pressure — hypertension in renal amyloidosis is indeed rare; next there was a rather small amount of albumin in the urine, a low albumin-globulin ratio and, finally, a gradually rising serum nonprotein nitrogen.

Balanced against all this clinical evidence is one miserable laboratory test — the Congo red test. They tell us that it showed 76 per cent of the dye remaining in the blood in an hour. When Bennhold<sup>1</sup> described this test in 1923, he claimed that normally less than 30 per cent disappeared from the blood in an hour and that in amyloid disease 40 to 100 per cent leaves the blood in an hour. It has been found by others, however, that 40 to 60 per cent may remain in the blood in cases of amyloid disease and in other types of nephrosis, so that it is not always of practical value in determining the type of nephrosis. Bennhold did not differentiate the response in the gross lardaceous type from that in the small atrophic contracted type of amyloid disease, and it is for this reason that I am going to stick to my diagnosis in the face of a 24 per cent removal of Congo red from this patient's blood. If he turns out to have had small kidneys with rather quantitatively small amounts of amyloid, then the test could still be consistent with the clinical evidence.

DR. BENJAMIN CASTLEMAN: Do you want to comment about the size of the spleen?

DR. CHAPMAN: I assumed that it was part of the whole process, that is, that he had an amyloid spleen.

DR. CASTLEMAN: Dr. Dameshek, you saw this patient before he entered the hospital. Would you like to add anything?

fectious hepatitis. There had been far too much pain, and there had been a rather rapid development of extremely severe jaundice. The course of the disease was quite unlike what one would expect in that condition. I have already mentioned that I do not believe that this was a toxic acute yellow atrophy. We are told that the patient had gallstones removed many years before, which brings up the question, Did this patient have a complication of the previous cholelithiasis? Did a stone, for instance, in the common bile duct cause all the present jaundice? There is nothing in the history that is against that diagnosis or that rules it out. On the other hand, that certainly does not explain some of the present findings — the ascites and the gastrointestinal bleeding. Cirrhosis would not be expected to give this degree of jaundice and to terminate in such a short period, ten or fourteen days.

We now come to the likeliest diagnosis — some form of neoplasm. Certainly in a person with a previous history of cholelithiasis we have learned in recent years to think of carcinoma of the gall bladder or of the bile ducts as a not uncommon cause of death in a person with jaundice. The diagnosis of carcinoma of the gall bladder or bile ducts is sometimes difficult. One cannot always palpate the mass in the gall-bladder region. That was the diagnosis that I favored until I came to the story of bleeding from the upper gastrointestinal tract. I must say that I was disappointed to read about that tarry stool.

Could this have been one of the most frequent causes of jaundice in a person of this age, namely, carcinoma of the head of the pancreas? There is nothing in the entire picture that rules out that diagnosis, except, again, the gastrointestinal bleeding.

Could this have been a primary hepatoma or a diffuse carcinomatosis primary in the liver? It could have been, except for the bleeding in the upper gastrointestinal tract. There is nothing else against it. Even the fact that they did not feel a solitary liver mass does not rule out the diagnosis.

We must bear in mind that about a month before she developed jaundice she had a nonproductive cough, diagnosed as due to bronchitis. Possibly that was indicative of metastases to the lungs. So we must think of some type of neoplasm below the diaphragm, with early metastases to the lungs and later metastases elsewhere. On the basis of statistical frequency, carcinoma of the stomach is the likeliest diagnosis. Certainly it would account for most of the findings — metastases to the lymph nodes compressing the bile ducts, metastases to the liver, spreading to the peritoneum and part of the cause of the accumulation of the fluid in the abdomen, metastases to the lungs, and gastrointestinal bleeding.

As for the terminal episode, I do not know how we can tell whether she had a bronchopneumonia

or a terminal pulmonary embolus. We are told nothing about the physical findings at the time. I think that terminal bronchopneumonia is far more frequent in a case like this.

I should say then that this patient had carcinoma of the stomach with metastases to the lymph nodes, compressing the bile ducts, and metastases to the liver, peritoneum and lungs, arteriosclerotic heart disease, passive congestion of the kidneys and terminal bronchopneumonia.

A PHYSICIAN: Do you attach any significance to the elevated prothrombin time in connection with the tarry stool?

DR. JACOBSON: We have no evidence of a bleeding tendency in other parts of the body, but I should guess that bleeding sufficient to have changed the color of the stool from clay to tarry could hardly have been the result of a high prothrombin time.

A PHYSICIAN: What about the possibility of carcinoma of the ampulla of Vater?

DR. JACOBSON: In referring to carcinoma compressing the bile ducts I include the ampulla of Vater or some other place in the biliary tract.

A PHYSICIAN: Would that not explain the tarry stool?

DR. JACOBSON: It might by erosion into the gastrointestinal tract. It is a good possibility.

DR. CHESTER M. JONES: I saw this patient when she was first admitted. She was comatose practically all the time after admission and obviously a hopeless case. I thought at the time that she had malignant disease involving the liver and that it was primary or secondary. I could see no way of establishing a diagnosis.

The stool was a glove specimen, and it was pitch black. It would seem to me that Dr. Jacobson's comment was correct: namely, one would anticipate frank ulceration of the mucosa to underlie bleeding of that extent. On the other hand, with pronounced jaundice of this degree, one often obtains positive guaiac tests in the stools regardless of the underlying cause of the jaundice — whether it is intrahepatic or extrahepatic. This stool was actually tarry. I reasoned as Dr. Jacobson did — that there was ulceration. An ulcer in the presence of a clinical picture like this would make me suspect that there was a new growth that had ulcerated into the stomach or the duodenum. Carcinoma of the ampulla may invade the duodenum with subsequent erosion. I thought that the findings were consistent with spreading neoplastic disease.

The death, I believe, even as it is described here, is not at all suggestive of bronchopneumonia or anything else but complete failure of the liver. This woman had enough liver damage to prevent normal function. It is entirely comparable with the sort of picture seen in terminal acute yellow atrophy. We had an excellent example in a case discussed here a short time ago; the patient had carcinomatosis of the liver and a similar death.

## CASE 31232

## PRESENTATION OF CASE

A sixty-seven-year-old woman was admitted to the hospital because of jaundice and drowsiness.

Three or four months before admission she complained of severe pain that appeared to involve the entire epigastrium. A month later she developed a severe nonproductive cough, which was diagnosed as bronchitis. Ten days before admission she became jaundiced and began to suffer from generalized pruritus. The jaundice and pruritus were progressive, although the degree of jaundice seemed to fluctuate. During the few days prior to entry she became increasingly drowsy and unintelligible.

Many years before entry she had had gallstones removed, but the gall bladder was not taken out.

Physical examination revealed an obese, drowsy, deeply jaundiced woman. The skin showed excoriations from scratching. The breath was "mousy." The few remaining teeth were carious. A Grade 2 systolic murmur was heard over the entire precordium. The heart was enlarged, extending by percussion 14 cm. to the left of the midsternum. The abdomen was distended and showed a definite fluid wave with shifting dullness. The liver was palpable three fingerbreadths below the costal margin. There was slight tenderness in the right upper quadrant of the abdomen. A rectal examination was negative. The ankles showed moderate edema.

The temperature, pulse and respirations were normal. The blood pressure was 112 systolic, 60 diastolic.

Examination of the blood showed 15.3 gm. of hemoglobin and a white-cell count of 16,400, with 72 per cent neutrophils, 22 per cent lymphocytes and 6 per cent monocytes. The red cells and platelets were normal. The urine was dark amber, with a specific gravity of 1.018, and gave a +++ test for albumin and a ++++ test for bile. The sediment showed 15 red cells, 75 white cells and occasional granular casts per high-power field. A stool was black and tarry and gave a ++++ guaiac test. The serum nonprotein nitrogen was 50 mg. per 100 cc., the phosphorus 2.8 mg., the icteric index 180, the prothrombin time 44 seconds (normal, 18 to 20 seconds), and the alkaline phosphatase 6.0 Bodansky units. The fasting blood sugar was normal.

The temperature rose to 101.0°F., and the pulse to 100, and the respirations quite abruptly rose on the third day to 35. The patient received intravenous glucose and vitamins, in addition to a high-carbohydrate, low-fat diet given through a nasal tube. She also received a whole-blood transfusion. The stupor deepened, and she quietly expired on the fourth hospital day.

## DIFFERENTIAL DIAGNOSIS

DR. BERNARD JACOBSON: I should like to make a few comments on some of the findings. Three or

four months before admission the patient complained of severe pain. I assume that it was not one episode of severe pain but the beginning of recurrent pain of several months' duration. We are not told anything about her appetite or her general sense of well-being, but since she was apparently well nourished when she came in, I assume that she did not lose much weight. We are told that the degree of jaundice seemed to fluctuate, which is of some interest. By and large, severe cases of catarrhal jaundice are apt to have less fluctuation of the degree of jaundice than do those with stone in the common duct or carcinoma of the head of the pancreas.

The breath was "mousy." This of course is of some significance because a mousy odor is due to the presence of certain amines from the liver cells, and that usually signifies diffuse atrophy. But it is fair to say that, although it is suggestive of diffuse atrophy of the liver, it is not pathognomonic. We are told farther on that the liver was palpable three fingerbreadths below the costal margin. In an obese woman of this age that may not mean enlargement at all. It may mean a liver that has been pushed down one or two fingerbreadths and be a perfectly normal-sized liver for such a person.

We are not told anything about other masses in the right upper quadrant. Certainly one would be looking for masses other than the liver. I should be interested to know if there was a mass that corresponded to the size, shape and position of the gall bladder. On the other hand, the fact that none was noted in a woman with an obese abdomen may not be of any significance. A liver palpable three fingerbreadths below the costal margin is certainly against the diagnosis of acute yellow atrophy. The preceding history of the case—jaundice of ten days' duration and rapid progress to death on the fourteenth day—is consistent with the diagnosis of acute yellow atrophy, but the presence of a liver that did not shrink in size is definitely against such a diagnosis. We are told later that the patient had a hemoglobin of 15.3 gm. I rather suspect that this patient's hemoglobin was less; she may have been dehydrated at the time the initial blood count was taken. Nonetheless, that is an important finding, because it rules out for further consideration of such a rare diagnosis as congenital hemolytic jaundice.

Rather upsetting to me, with my preconceived opinion of what this case might have been, is the report that the stool was black and tarry. It seems to me that it would take a lot of blood to color a stool black, especially one that should have been rather light in color because of the absence of much bile pigment. It could not have been due to a recent hemorrhage. That is the first indication that there had been bleeding high in the gastrointestinal tract.

I believe that we can dismiss several of the common causes of jaundice in a person of this age. It certainly was not catarrhal jaundice or diffuse in-

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## INCREASING OPPORTUNITIES FOR WOMEN IN THE MEDICAL SERVICES

THE opening at Camp Edwards of a 6000-bed reconditioning hospital for wounded and sick veterans is a reminder that the healing of the wound is only a stage in the long process of treating the disabled. This sequence of events may be dramatically initiated with the administration of plasma; it is not finished until the highest possible degree of function is regained, a hopeful attitude toward life is restored, and a new skill, if necessary, is developed.

The amazingly high percentage of lives of wounded soldiers that are now being saved is a modern miracle of science, but it carries with it a great and

continuing responsibility—that of making as many as possible of these bodies useful to their tenants and to mankind, and of reducing to a minimum the permanent human wreckage that war always leaves in its wake.

Certain accessory medical services are largely instrumental in the attainment of such goals, and in these services, women are playing the leading parts. Bulletin 203 of the Women's Bureau, United States Department of Labor, describes the present situation as regards physical and occupational therapy, and the strides that these services have taken as a result of the war.

As the bulletin so aptly phrases it, physical therapy is a relatively new occupation in which an old art is plied—that of treating human ailments with heat, light, water, exercise and other physical means. Even greater progress in the development of this service for the future seems assured by the recent Baruch gift for research and specialized training for physicians in the field of physical medicine.

Physical therapists, more numerous than occupational therapists although still fewer than medical laboratory technicians, numbered before the war some 3100, of whom less than 50 were men. Sixteen approved institutions were then graduating about 150 women a year. Thirty-one institutions, including eight army hospitals, now maintain schools of physical therapy, and graduated over 700 technicians in 1944, representing a considerable increase, although a number still far short of the needs for military, veterans' and rehabilitation services.

The occupational therapist, as distinguished from the physical therapist,

... conducts programs for patients confined in hospitals and other institutions to provide them with directed activity and to assist in their rehabilitation; plans and organizes work projects for patients; supervises workers who teach and direct patients in assigned activities, ... studies patients' reactions while they are engaged in work situations, and writes reports describing their conditions.

Something under 2000 occupational therapists, registered and unregistered, were practicing by 1940; five approved schools were listed in 1941, a number that had grown to twenty-one in 1944. Ninety-nine per cent of occupational therapists are women.

All it implies is that the liver is profoundly damaged and that the patient finally dies of hepatic failure. If one had done blood chemistry determinations one would have found that terminally there was some superimposed renal failure.

#### CLINICAL DIAGNOSIS

Carcinoma of head of pancreas.

#### DR. JACOBSON'S DIAGNOSES

Carcinoma of stomach, with metastases to lymph nodes, compressing bile ducts, and to liver, peritoneum and lungs.

Bronchopneumonia, terminal.

Arteriosclerotic heart disease.

Passive congestion of kidneys.

#### ANATOMICAL DIAGNOSES

Hepatoma, with metastases to lungs, adrenal glands and vertebrae.

Jaundice.

Ascites.

Obstructive cirrhosis of liver.

Acute pancreatitis.

Cholelithiasis.

Dilatation of common bile duct.

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy showed about half a liter of straw-colored fluid in the abdomen. There were no peritoneal implants. The liver was large, weighing 2350 gm. About 90 per cent of the parenchyma of the right lobe and 50 per cent of that of the left lobe were replaced by grayish-white nodules from 0.5 to 10 cm. in diameter. The intervening tissue was green. This gross appearance was consistent with a diffuse metastatic process. We looked carefully throughout the body for a primary source but were unable to find one. The stomach showed no erosions, and there were no gross erosions anywhere in the entire intestinal tract. I cannot explain the tarry stool except on the basis of jaundice. Small nodules, 2 or 3 mm. in diameter, were found in the adrenal glands and in the lungs, and most of the vertebral bone marrow was replaced by tumor. With this degree of bone-marrow metastasis it is surprising that the alkaline

phosphatase was not elevated and also that there was no anemia.

The liver parenchyma between the tumor nodules showed bile stasis and biliary obstructive cirrhosis. There were no enlarged lymph nodes compressing the extrahepatic bile ducts, but certainly the intrahepatic ducts were compressed and undoubtedly accounted for the jaundice; they may not, however, have accounted for the cirrhosis. The gall bladder did contain a stone, and the common bile duct was dilated, indicating that stones had been passing down for some time. In the head of the pancreas was an ill-defined 2-cm. area of acute inflammation, with foci of fat necrosis. This is further evidence that the stones had been going down the bile duct. I am just wondering whether some of the symptoms that this patient had, especially the pain, rather than being due to the hepatoma itself, might have been due to stone in the common duct that blocked the pancreatic duct and set off a pancreatitis that smoldered along.

DR. FRANCIS D. MOORE: How big was the stone in relation to the caliber of the cystic duct?

DR. CASTLEMAN: The stone measured about 0.5 cm. in diameter, and the duct measured up to 3 cm. in circumference. At some time, a stone could have become impacted in the ampulla at the entrance to the pancreatic duct, thus starting up an acute pancreatitis. I think that that is the best bet and that the jaundice was a combination of extrahepatic and intrahepatic bile-duct obstruction, although there was no stone in the common bile duct or pancreatic duct at the time of autopsy.

DR. JONES: It is rather surprising that with so much carcinomatous involvement she did not have a long period of jaundice.

DR. CASTLEMAN: Certainly more than half the liver was involved.

DR. JONES: It is also interesting that there was a striking family history of carcinoma. Various members of the family had died of carcinoma.

DR. MILFORD D. SCHULZ: Was the spleen normal?

DR. CASTLEMAN: It was small.

DR. SCHULZ: And the esophageal veins?

DR. CASTLEMAN: They were not enlarged. There was not much portal obstruction. The tumor had invaded the hepatic veins throughout the liver, which accounts for the metastases to the lungs.

countries. It is hoped, moreover, that after the war Great Britain will see fit to set up a medical library association on the lines similar to the associations so well established in America.

Medical bibliography is greatly indebted to Morton for his splendid publication, but in a field that is continually advancing one can only hope that his book will be considered as a steppingstone toward future publications along the same lines. Indeed, Morton himself expresses a similar opinion when he hopes that his book "may be considered worthy to serve as a starting point for something better, to the construction of which both the specialized knowledge of the medical historians and the bibliographical skill of the librarians can at some future date be devoted."

#### REFERENCES

1. Texts illustrating history of medicine in Library of Surgeon-General's Office. *Index-Catalogue of the Library of the Surgeon-General's Office* 2 S., 17:89-178, 1912.
2. Garrison, F. H. *An Introduction to the History of Medicine*. Fourth edition. 996 pp. Philadelphia: W. B. Saunders Company, 1929.
3. *Ibid.* Revised students' check-list of texts illustrating history of medicine, with references for collateral reading. *Bull. Inst. Hist. Med.* 1:333-434, 1933.
4. Garrison, F. H., and Morton, L. T. *A Medical Bibliography: A check-list of texts illustrating the history of the medical sciences*. 412 pp. London: Grafton and Company, 1943.

### MASSACHUSETTS MEDICAL SOCIETY

#### DEATHS

ANSHIN — Marcus M. Anshin, M.D., of Lynn, died May 21. He was in his fifty-third year.

Dr. Anshin received his degree from Loyola University School of Medicine, Chicago, in 1919 and did postgraduate work in Vienna and Berlin. He was a fellow of the American Medical Association.

His widow, a daughter and a sister survive.

FRASIER — Joseph A. Frasier, M.D., of New Bedford, died May 20. He was in his seventieth year.

Dr. Frasier received his degree from Columbia University College of Physicians and Surgeons in 1896.

His widow, a son and two sisters survive.

HURLBUT — Lt. Robert S. Hurlbut (MC), U.S.N.R., formerly of Cambridge and Marblehead, was killed in action March 26 when the destroyer *Halligan* was sunk off Okinawa. He was in his thirty-fourth year.

Dr. Hurlbut received his degree from Harvard Medical School in 1938 and was permanent secretary of his class. He was called to active duty in July, 1942, after serving two years as a surgical house officer at the Massachusetts General Hospital. Following service at the Chelsea Naval Hospital at the Office of Medical Officer Procurement, First Naval District, and as physician at the Harvard Naval Dispensary, he began sea duty on the *Halligan* in September, 1943. He saw service in the Atlantic and in North Africa, and was in invasion actions for more than a year in the Pacific.

His mother, his widow and four children survive.

LEVIN — Harry M. Levin, M.D., of Malden, a surgeon in the United States Public Health Service Reserve, was killed on January 29 when the ship he was on was torpedoed at Guadalcanal.

Dr. Levin had been on active duty with the United States Coast Guard since February, 1943. He was first assigned to stations on the West Coast and since September, 1944, had been on sea duty in the South Pacific.

His widow and three children survive.

### CORRESPONDENCE

#### POSTWAR POSITIONS FOR ANESTHESIOLOGISTS

*To the Editor:* The Hospital Section of the Postwar Planning Committee of the New England Society of Anesthesiology would like to hear from physicians who are interested in the peacetime practice of anesthesiology in New England. This information will be made available to persons interested in obtaining the services of an anesthesiologist in private, group or hospital practice in New England. It is thought that the collection and dissemination of this information may facilitate the proper relocation of anesthesiologists now in the service when they return to civilian practice.

The following information is desired from those who are interested: age, medical school, year of graduation, internship (year and hospital), training in anesthesiology (in detail, giving length and type of training and chief of service), activity and specialty after completion of training, military experience in anesthesia, publications, membership in medical societies, present address and permanent address.

This information should be sent to me as chairman of the committee. The other members are Drs. Jacob H. Fine and Sidney C. Wiggan.

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### BOOK REVIEWS

*Ourselfs Unborn: An embryologist's essay on man.* By George W. Corner, M.D. 8°, cloth, 188 pp., with 18 illustrations. New Haven, Connecticut: Yale University Press, 1944. \$3.00.

Here is a book that everyone who is interested in life itself will want to read and to own. It is a scholarly, practical and intensely interesting account of the biography of the first few weeks of life. The distinguished author, who is director of the Department of Embryology, Carnegie Institution, Washington, D. C., and professor of embryology at Johns Hopkins University School of Medicine, presents his subject matter in a pleasant and facile style; here and there he infuses his discussion with provocative quotations from the history of embryology, philosophy, poetry and religion. Yale University was indeed fortunate in choosing Dr. Corner to give the Terry Lectures, which constitute this book. In presenting an account of the natural history of the human embryo, he shows how science can contribute to the broadening and purification of religion itself.

The first lecture considers the topic "The Embryo as Germ and as Archive," and the author concludes this lecture with the following paragraph: "Thus to the seeing eye the human embryo from egg to birth is an archive in which is written the evidence of its descent as an animal, a vertebrate, an amniote, a mammal, a primate; and it is an organic germ, in which the gift of life is intrinsically bound up with the necessity of growth and of ineluctable change. This is not only preparation for life; it is life itself." The second lecture is titled "Prenatal Fate and Foreordination." The author presents the problem of embryonic defect and death in the human species and makes it clear that in man, as in other animals, genetic and constitutional factors are operative in some cases, and disturbances of the maternal environment in others, in the production of prenatal damage and loss. The embryologist sees the human egg as endowed with a general property of organic creatures, and he would never have conceived the idea that an immaterial self-conscious existence is entrusted to the uncertain custody of the human egg. The author declares his conviction that the spirit of man — all that makes him more than a beast and carries him onward with hope and sacrifice — comes not as a high-born tenant from afar but as a latent potentiality of the body. It is true to a



Although the care of war casualties has, of course, opened up unlimited opportunities for these medical services employing women, they need have no fear of facing any serious postwar depression. The country will need these relatively new professional groups so long as it continues to expect a high grade of medical practice and hospital care.

## MEDICAL BIBLIOGRAPHY

MUCH of modern medicine stems from Sir William Osler, and in the later years of his life, one of his principal interests was medical history and medical bibliography. He stimulated the late Fielding H. Garrison, of the Army Medical Library, to make out a list of the most important contributions to the literature of medicine and its ancillary sciences, to show the significance of individual writings in the history and development of the medical sciences. This list<sup>1</sup> first appeared in 1912, and since it was considered by Garrison "as a convenient scaffolding for a book," he later wrote his famous *An Introduction to the History of Medicine*,<sup>2</sup> a standard work invaluable to all students of the subject. When Garrison moved to Baltimore to become librarian of the Welch Medical Library, he expanded the list and republished it in 1933 under the title "Revised Students' Check-List of Texts Illustrating the History of Medicine, with References for Collateral Reading."<sup>3</sup> In the last ten years, a further revision with additions and annotations was undertaken by Mr. Leslie T. Morton, the librarian of St. Thomas's Hospital Medical School in London. This important and outstanding reference work has now been published.<sup>4</sup>

Garrison's revised check-list contained 4186 entries; Morton has retained 3826 and has added 1680 new bibliographical notes. Some of the additions are to the important contributions made between 1933 and 1943, but many of the other sections have been expanded, with the idea of showing the significance of the entries more clearly. In addition, Morton has provided an author and subject index. The majority of references have been verified, and many minor corrections have been made. In a few instances, owing to the war, it was not possible for Morton to see the original publication, but he

has fortunately had the help and advice of friends in checking references that were not available to him in London or in other British library centers.

The list as published by Morton is extraordinarily complete and accurate. Its bibliographical matters, such as the spelling of names, the dates of birth and death of the author, the exact names of secondary contributors and the title and notes on the contents of each paper, sometimes not clear from the title, are features of this work for which only a trained librarian with a bibliographical instinct could be responsible.

The matter of how much to say about each contribution is something most difficult to decide, particularly in relation to a publication of recent date. No one, for instance, would question the propriety of putting in the paper by Lawrence O'Shaughnessy in 1936 on an experimental method of providing a collateral circulation for the heart as an outstanding contribution to medical advancement. That O'Shaughnessy, as stated by Morton, was killed in Flanders in May, 1940, while serving with the R.A.M.C., although important biographically, is of slighter value from the point of view of bibliography. The same might be applied to the note regarding John Locke's "Essay" stating that it occupied him off and on for twenty years. When Morton writes, however, that a book published in 1575 in Spanish, which is difficult to obtain, was translated and issued in 1696 in English, or that a publication of 1690 was reprinted in 1910, he is indeed giving important information and something that every student of medical history will welcome. The matter of inclusion or notation, however, is largely a question of individual preference. Even if an international commission of medical historians should meet, there would, no doubt, be many instances of disagreement.

Morton's list is of such importance that it would seem worth while to go beyond an individual compiler and to suggest further revision under the auspices of a combined British and American medical historical commission. Such an endeavor might well be the concern of the Medical Library Association in America and the National Medical Library in Washington, along with a nucleus of medical librarians in Great Britain and possibly in other

this belief in the adaptation of nature to man and further to indicate its purpose. The author has marshaled his facts rather well and has drawn them from the fields of the solar system and of the chemistry of the atmosphere and the ocean, as well as from the fields of evolution and the physiologic adjustment in animals including man.

Emphasis is laid on the points that there is directive purpose lack of everything and that this purpose is being carried out by a supreme being whom we call God. The high quality of science has always been to find a fact, and although science disclaims any desire to search for God, it is nevertheless true that men of the stamp of Copernicus, Darwin and others had deeply religious feelings. This book gives some support to the idea that only deeply religious people of our largely material age are the earnest men of science. It is perhaps in this sense that the book will make a strong appeal to general readers. The reviewer believes that the author offers reasonable testimony in the way of facts for his thesis that man does not stand alone — a keen challenge to Julian Huxley's book *Man Stands Alone*.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Endocrinology: A brief review for physicians.* 12°, paper, 169 pp. Circular No. 177. *Heart Disease: An elementary reference for physicians.* 12°, paper, 63 pp. Circular No. 176. Published by the Department of Public Health, State of Illinois, Roland R. Cross, M.D., director.

These two elementary manuals on common disorders are published as part of the postgraduate medical education program of the Department of Health of Illinois. The department has felt the need of bringing advances in diagnosis and therapy to practitioners and consequently has adopted the plan of preparing brief summaries in various fields of medicine for distribution to all physicians in Illinois. It is hoped that through this service the busy doctor can keep himself up to date with a minimum of effort and without taking any time away from his practice.

*Organic Chemistry.* By Louis F. Fieser and Mary Fieser. 8°, cloth, 1091 pp. Boston: D. C. Heath and Company, 1944. \$8.00.

This new textbook has been made useful to physicians by the inclusion of a number of chapters dealing with significant applications of organic chemistry to the biologic and medical sciences. The presentation is in a readable narrative style, with an extensive body of factual data included in the form of comprehensive tables and citations under formulas. It is an up-to-date comprehensive authoritative text in its field.

*The Sick African: A clinical study.* By M. Gelfand, M.B., Ch.B., M.R.C.P., D.M.R., Government Medical Service, Southern Rhodesia, medical officer, Salisbury Native Hospital, physician to the War Emergency Hospital, government pathologist, Pasteur Institute and Public Health Laboratory, Salisbury. With a foreword by Colonel A. P. Martin, O.B.E., M.D., D.P.H., D.T.M. and H., director of medical services, chief health officer and medical director of Southern Rhodesia. 8°, cloth, 373 pp., with 123 illustrations. Cape Town, South Africa: Post Graduate Press, in association with Stewart Printing Co., Ltd., 1944. 25 shillings.

This clinical manual has been written for the members of the medical profession who practice among the African natives. It is hoped that it will also be of assistance to missionaries and native medical orderlies. The descriptions of diseases have not been gone into in great detail, but an endeavor has been made to stress the salient features of the diseases so that the physician will be able to recognize them without difficulty. Many of the clinical manifestations of disease in the native differ from those of the same diseases in the European, and these differences have been discussed in the light of medical men who have practiced among the natives. The civilization and the outlook of the native in no way resemble

those of the European. This fact must be taken into account, for it involves an entirely different angle of approach in investigation and treatment. There are also practical difficulties that should be considered, such as the long distances to be covered, the lack of facilities and the insufficiency of funds available for medical purposes. Much of the detail of helminthology, protozoology and parasitology has been purposely omitted. The author has endeavored to show how best to treat the patient in the most practical and simple way, without losing sight of the difficulties of native practice. Each disease has been discussed in a separate chapter without regard to classification. Colonel Martin in his foreword characterizes the manual as an outstanding work that should meet the needs of all workers in the African field of tropical medicine.

*Physiology in Health and Disease.* By Carl J. Wiggers, M.D., D.Sc., professor of physiology and director of the Physiology Department, Western Reserve University School of Medicine, Cleveland. Fourth edition. 8°, cloth, 1174 pp., with 246 illustrations. Philadelphia: Lea and Febiger, 1944. \$10.00.

The fourth edition of this standard textbook, first published in 1934, has been thoroughly revised and brought up to date in accordance with developments resulting from the war. To keep the book within a reasonable size and to include a great amount of new material, many topics and sections have been rearranged, rephrased and condensed or printed in small type. Many portions have been greatly enlarged, and several new chapters have been included. Approximately one third of the text has been completely rewritten; over a thousand new references to pertinent literature have been added, and the number of illustrations has been increased. Particular attention is called to new or expanded portions dealing with war physiology, for example, discussions of nerve regeneration, eye fatigue, color appreciation, somatic and visceral pain, headache, blood and plasma depletion, principles of transfusion, blood substitutes, blood volume, hemorrhage and shock, abnormalities of blood coagulation, artificial respiration, pulmonary edema, dietary deficiencies, undernutrition and starvation, muscular exercise, physical fitness and fatigue, water deprivation, acclimatization and aviation physiology, with particular emphasis on the effects of pressure changes, anoxia, acceleration and the role of proprioceptor, vestibular and ocular reflexes in flying. Altitude-sickness, airsickness and seasickness are likewise discussed.

*Dr. Colwell's Daily Log for Physicians: A brief, simple, accurate financial record for the physician's desk.* 8°, cloth. Champaign, Illinois: Colwell Publishing Company. \$1.00-\$5.00.

This standard account book, especially designed for physicians, should meet the needs of most practitioners. It constitutes a complete system of financial records, with the exception of the ledger. Any form of ledger may be used in conjunction with the *Daily Log*. The space provided accommodates an average practice for a calendar year. For physicians with large practices, however, an edition is issued in two volumes, providing double the space for each day.

*Theory of Occupational Therapy.* By Norah A. Haworth, M.A. (Cantab.), M.R.C.S., L.R.C.P., D.P.M., assistant medical officer, London Passenger Transport Board; and E. Mary Macdonald, principal, Dorset House School of Occupational Therapy, Barnsley Hall Emergency Hospital, Bromsgrove. With a foreword by Sir Robert Stanton Woods, M.D., F.R.C.P., consultant adviser in physical medicine, Ministry of Health, and physician in charge of the Department of Physical Medicine, London Hospital. Second edition. 8°, cloth, 148 pp., with 68 illustrations. London: Baillière, Tindall and Cox, 1944. \$2.50.

In the preparation of this second edition of a manual intended for students and nurses, the text has been thoroughly revised. A considerable amount of new material has been added, especially in the chapter on occupational therapy in a general hospital and also in that on the treatment of cardiac cases and arthritis. The first four chapters discuss the treatment of mental disorders, orthopedic and surgical cases, cardiac diseases and tuberculosis. The remaining chapters deal with equipment, records, finance and training. A bibliography of seven pages is appended to the text.

certain extent that the fate of the embryo is foreordained. The third lecture deals with the subject "The Generality and the Particularity of Man." The author indicates that the embryologists could hardly fail to support the most orthodox Darwinian-Huxleyan doctrine of the descent of man from an ape-like ancestor, in close relation with the gorilla and the chimpanzee. Readers will be interested in the concept of man's nature as a "Diagram of the Ladder," a point of view closely interwoven with the older thought of Christianity and the concept of the "Diagram of the Fan," which expressed the findings of evolutionary biology.

The reviewer strongly urges every educated person to read this book and thereby add to his intellectual stature.

*The Analysis and Interpretation of Symptoms.* Edited by Cyril M. MacBryde, M.D. 8°, cloth, 301 pp., illustrated. Philadelphia: J. B. Lippincott Company, 1944. \$9.00.

The striking feature about modern medicine is its increasing emphasis on the physiologic processes, and the trend is toward dynamics rather than static description. Physiologic principles are emphasized not only in the treatment and prevention of disease but also in its diagnosis as well. No longer is it stressed that such and such signs spell a certain medical syndrome, but rather one attempts to understand the changes in a particular case that deviate from the normal. With this view in mind, one can evaluate this book, which is a symposium by a group of prominent specialists, who analyze a small group of frequent symptoms and signs. The discussions are logically and well presented, and the conclusions in many of the papers are often summarized in one or two sentences. As in any book, there are statements with which one can take issue.

As a whole this book will prove valuable to those who would keep abreast of modern medicine, with its physiologic trends and its chemical analyses, which are great aids in diagnosis and tend to supplant that nebulous quality — the clinical sense — which will always have its place in medicine.

*The Pathogenesis of Tuberculosis.* By Arnold R. Rich, M.D. 4°, cloth, 1008 pp., with 89 illustrations, 20 tables and 4 charts. Springfield, Illinois: Charles C Thomas, 1944. \$10.50.

This monumental book is the culmination of the many fruitful years of labor that Dr. Rich has devoted to the pathology of tuberculosis. In the preface, the author states that the purpose of the book is to present the basic factors and principles that influence the occurrence of tuberculous infection and determine its progression or arrest. In his own words, the object has been "to determine the influence of each of those factors upon the pathogenesis of the disease and to correlate into a unified whole the basic interdependent, but at present often isolated, facts that have been given to us by bacteriology, immunology, pathology, clinical observation, experimental investigation, epidemiology and genetics."

In the twenty-one chapters, the writer does just that, and after reading through this book one stands both in awe and in amazement at the thoroughness with which this has been accomplished. He draws not only on his own rich experience but also on the vast amount of literature for the purpose of bringing the reader up to date on the best thoughts and opinions in the diversified fields of pathology and immunology in tuberculosis.

The reader will be well rewarded by referring to the chapters on the bacteriology of the tubercle bacillus, with a full discussion of its chemical constituents and the variations in its forms and virulence, as well as its modes of infection. The greater part of the book deals with pathogenicity versus immunology, and the problems of epidemiology and of individual, native and tissue resistance are thoroughly discussed. No clinician can afford to miss the scholarly dissertations on the mechanism of hypersensitivity and on desensitization and its relation to the characteristics of tuberculous lesions and symptoms.

Despite the formidable and intricate discussions, the style is smooth and the subject matter is presented in a clear and orderly manner. The short summaries at the end of each chapter are extremely helpful. The illustrations are adequate and are beautifully reproduced. As a reference book on the pathogenesis of tuberculosis, the reader will find it complete, concise and authoritative. The clinician, pathologist, bacteriologist and public-health worker should find the book useful and also stimulating.

*Technic of Electrotherapy and Its Physical and Physiological Basis.* By Stafford L. Osborne, M.S., Ph.D., and Harold J. Holmquest, B.S., B.S. (M.E.). 8°, cloth, 780 pp., with 240 illustrations and 72 tables. Springfield, Illinois: Charles C Thomas, 1944. \$7.50.

The authors of this book were evidently under the impression that medicine is both a science and an art and that electrotherapy, being a branch of medicine, should be treated with regard to these two forms of culture. Accordingly they do not confine themselves to mere statement of facts but present a scheme of laboratory tests to prove the authenticity of their claims for almost every method of treatment. The system of laboratory experimentation that is outlined in this book has all the earmarks of scientific precision and artistic form.

Although the authors state in the preface, "This text . . . is not to replace the clinical textbooks now available," the reviewer believes that it compares favorably with any one of them. The fact that it constantly stresses the rationale for choosing a certain physical measure in a given case, based on a familiarity with the underlying electrophysics and electrophysiology, tends rather to add than to detract from its clinical value.

Another praiseworthy feature of this work is the arrangement of its subject matter in a manner that will suit two classes of readers — the busy general practitioner and the specialist or teacher in this field. The former may have neither the time nor the desire to trace each case to its fundamentals in physics, chemistry, mathematics and mechanics. For him the essentials are stated with simplicity. On the other hand, the man who takes more than a lukewarm attitude to the subject will find a plentiful supply of data, references, curves, tables, charts, cuts and diagrams to illustrate, clarify and prove the soundness of the statements that are made by the authors. By way of illustration the book contains a table of logarithms and one of trigonometric functions of an angle. These do not concern the average reader of an electrotherapeutic text and are never found in one. On the surface they may seem to be out of place, but in reality they are part and parcel of those portions of the book that were written for the more profound students of electrotherapy.

On the whole this book is quite different from the usual textbooks on the subject, almost a stranger in their midst, but paraphrasing Shakespeare, one might say: "As a stranger bid it welcome."

*Functional Disorders of the Foot: Their diagnosis and treatment.* By Frank D. Dickson, M.D., and Rex L. Diveley, M.D. Second edition. 8°, cloth, 352 pp., with 202 illustrations. Philadelphia: J. B. Lippincott Company, 1944. \$5.00.

In this book the authors have described clearly and concisely the common disabilities of the foot. There is a decided improvement in this second edition both in the arrangement of the material and in the subjects that are considered. The book is excellently illustrated with line drawings and photographs. It is well written, and the suggestions for treatment are in accord with recognized orthopedic practice.

A book of this sort is timely and should help greatly in arousing interest in a large number of disabilities that are now frequently neglected. The classification of functional disabilities is probably too simple for extensive use. One would like to see more emphasis placed on the muscular faults of the foot, which are so commonly encountered in both children's and adult's clinics. The bibliography at the end of the book has not been revised to include many of the newer contributions in medical literature. But these are minor faults. The book can be recommended unreservedly as the most practical treatise on disabilities of the feet in the English language.

*Man Does Not Stand Alone.* By A. Cressy Morrison. 12°, cloth, 107 pp. New York: Fleming H. Revell Company, 1944. \$1.25.

Through the centuries from Galen, Cicero, Paley and others, detailed arguments have been set forth to show the remarkable adaptation of man to nature. Since the beginning of the twentieth century there have been equal efforts to show the adaptation of nature to man. The present book, written by a scientist, purports to bring to the attention of thinking people the f

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## PSEUDODOXIA PEDIATRICA\*

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NEW YORK CITY

ALMOST three hundred years ago, Sir Thomas Browne wrote a treatise comprising seven books entitled *Pseudodoxia Epidemica or Enquiries into very many received Tenents and commonly Presumed Truths*. In this work he analyzed numerous fallacies generally accepted as truths in his day and demonstrated their absurdity.

The superstitions and magic rites that prevailed in the seventeenth century have been largely forgotten. But in the present scientific era, as well, theories and practices persist in medicine even though their falsity is patent or has been demonstrated. It is my purpose in this paper to inquire into some of the current pediatric errors and to analyze the reasons why they persist.

Notable progress in child care has been made since the turn of the century, and the results are strikingly registered in the greatly reduced morbidity and mortality rates for infants and children. Advances in medicine are made not only by the discovery of new principles, new information and new technics but as well by the discarding of false teachings and practices. One recalls how only a few years ago babies' mouths were meticulously cleansed, presumably to remove germs, and how the symmetrical ulcers of the palate, still occasionally seen, resulted. Even more recent was the discovery that mineral oil dropped into the nose, almost a routine procedure among well-cared-for babies a few years ago, may lead to pneumonia. One may mention here also vigorous removal of the vernix caseosa as an etiologic factor in impetigo of the newborn.

That early operative interference in empyema and osteomyelitis is contraindicated has been well established. Unfortunate was the patient of thirty years ago whose attending physician was alert and conscientious and recognized empyema early in its development. It is now known that over-rigid feeding schedules fostered parental overanxiety and frequently led to anorexia in young children.

These are practices that have come to be recognized as erroneous and that have been, in the main, abandoned. But there remain many others, equally erroneous and harmful, that continue in everyday use.

### TONSILLECTOMY

Prominent among these unwise practices is indiscriminate tonsillectomy. This subject will not be discussed in detail, since it has already been thoroughly examined by Kaiser,<sup>1</sup> Brennemann,<sup>2</sup> Graeme Mitchell<sup>3</sup> and others.<sup>4</sup> Attention may be called to the facts that mortality from the operation is by no means negligible, about 80 persons dying each year in the United States as a result of the anesthesia administered for this operation (Table 1).

TABLE 1. *The Number of Deaths in the United States Associated with Anesthesia*

YEAR	TOTAL NO. OF DEATHS	NO. OF DEATHS ACCOMPANYING TONSILLECTOMY AND ADENOIDECTOMY
1922	513	87
1923	474	80
1924	598	73
1925	677	116
1926	654	108
1927	695	112
1928	569	89
1929	690	100
1930	702	91
1931	678	86

and an equal number in England, where chloroform is widely used<sup>5</sup>; that the morbidity from pneumonia, lung abscess, hemorrhage and sepsis is considerable; that the etiologic relation of tonsillectomy to bulbar poliomyelitis is well established<sup>6-11</sup>; and that the operation may be an exciting factor in the anxiety neurosis of children.<sup>12</sup>

A convincing demonstration of the absurdity of indiscriminate tonsillectomy was given ten years ago by the American Child Health Association.<sup>13</sup> It surveyed a group of 1000 children, eleven years of age, from the public schools of New York City and found that 61 per cent of these had had their tonsils removed (Fig. 1). The remaining 39 per cent were subjected to examination by a group of phy-

\*From the Department of Pediatrics, New York University College of Medicine, and the Children's Medical Service, Bellevue Hospital.  
Presented at a meeting of the American Pediatric Society, Atlantic City, New Jersey, September 27, 1944.

†Associate professor of pediatrics, New York University College of Medicine.

*Modern Clinical Syphilology: Diagnosis, treatment and case study.* By John H. Stokes, M.D., professor of dermatology and syphilology, School of Medicine and Graduate School of Medicine, University of Pennsylvania, director, Institute for the Control of Syphilis, University of Pennsylvania, and member, Commission on Syphilis and Cognate Diseases, League of Nations Health Organization; Herman Beerman, M.D., Sc.D. (med.), assistant professor of dermatology and syphilology, School of Medicine and Graduate School of Medicine, University of Pennsylvania, assistant director, Institute for the Control of Syphilis, University of Pennsylvania, dermatologist, Philadelphia General Hospital, and dermatologist and syphilologist, Pennsylvania Hospital; and Norman R. Ingraham, Jr., M.D., assistant professor of dermatology and syphilology, School of Medicine, University of Pennsylvania, associate director, Institute for the Control of Syphilis, University of Pennsylvania, chief, Division of Venereal Disease Control, Philadelphia Department of Public Health, and chief, Syphilis Clinic, Philadelphia General Hospital. Third edition. 8° cloth, 1332 pp., with 911 illustrations. Philadelphia: W. B. Saunders Company, 1944. \$10.00.

The first edition of this outstanding work was published in 1926, and the second in 1934. Ten years having elapsed, it was considered advisable, even under wartime conditions, to bring out this third edition. Approximately 65 per cent of the text has been rewritten. The penicillin chapter and the account of syphilis in public health and military medicine are new. The chapter on prenatal, now largely congenital, syphilis, has been expanded and rewritten. The progress of serologic diagnosis has been reflected in extended space devoted to the biologic false-positive reaction. Every important technic of treating syphilis receives full detail and practical discussion. The attempt to write for the student, the practitioner and the specialist simultaneously really telescopes three books into one. In order to keep down the size of the book much use of small type has been found necessary. Likewise it has been found impossible to incorporate full bibliographic references. The book is highly recommended to all those who come in contact with syphilis in their daily work and for all medical libraries.

*Soldier to Civilian: Problems of readjustment.* By George K. Pratt, M.D., psychiatric examiner, United States Armed Forces, Induction Center, New Haven, Connecticut. With a foreword by George S. Stevenson, M.D., medical director, National Committee for Mental Hygiene. 8°, cloth, 233 pp. New York: Whittlesey House, 1944. \$2.50.

The author is a practicing psychiatrist with military experience and service on the staff of the Mental Hygiene Committee. He has made a careful study of the problems of the serviceman's readjustment. This manual has been written for the lay person who will be faced with these problems when the serviceman is discharged from the military service. In simple language, sensible advice and concrete suggestions are given on how to handle such problems as family life, marital relations, community position and occupational adjustment. Particular attention is directed to the man who returns with a physical or psychiatric handicap. An appendix contains the first outline formulated by the newly created National Committee for Service to Veterans, entitled "Community Service for Veterans: A guide to planning and coordination."

*Clinical Practice in Infectious Diseases: For students, practitioners and medical officers.* By E. H. R. Harries, M.D. (Lond.), F.R.C.P., D.P.H., medical superintendent, North-Eastern Hospital (London County Council), and Milroy Lecturer, Royal College of Physicians; and M. Mitman, M.D. (Lond.), M.R.C.P., D.P.H., D.M.R.E., medical superintendent, River Hospitals. With a foreword by W. Allen Daley, M.D. (Lond.), F.R.C.P., D.P.H., medical officer of health, London County Council. Second edition. 8°, cloth, 570 pp., with 52 illustrations and 26 tables. Edinburgh, Scotland: E. and S. Livingstone, 1944. \$6.00.

The text in this second edition of a work primarily intended for students and first published in 1940 has been thoroughly revised and much new material incorporated throughout the book. The size of the book has been increased by over a hundred pages, and selected references to medical literature lacking in the first edition have been appended to each chapter. This manual has considerable value for ready reference, although it is based on English practice.

## NOTICES

### ANNOUNCEMENTS

Dr. Isadore Green announces the removal of his office from 636 Beacon Street to 483 Beacon Street, Boston.

Dr. Miriam S. Udin announces the removal of her office from 636 Beacon Street to 483 Beacon Street, Boston.

### BOSTON DISPENSARY

A clinical staff meeting of the Boston Dispensary will be held at the Pratt Hospital Auditorium on Monday, June 11, at 12:30 p.m. Dr. Chester S. Keefer will speak on the subject "Use of Penicillin." Luncheon will be served at 12 noon.

### NEW ENGLAND PEDIATRIC SOCIETY

There will be a meeting of the New England Pediatric Society on Wednesday, June 13.

#### PROGRAM

12:00-1:00 p.m. Clinicopathological conference, Children's Hospital.

2:00-3:30 p.m. Clinic, Children's Hospital. Dr. Richard M. Smith and associates.

4:00-5:30 p.m. Clinic, Children's Center, 244 Townsend Street, Roxbury. Dr. Marian Putnam and associates.

6:30 p.m. Refreshments, Longwood Towers.

7:30 p.m. Dinner, Longwood Towers.

8:00 p.m. Behavior Problems in Childhood. Dr. Harry Bakwin, associate professor of pediatrics, New York University, New York City.

Members of the medical profession and students are cordially invited to attend the 8:00 p.m. meeting.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 14

##### FRIDAY, JUNE 15

\*9:00-10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Hemangioma. Dr. G. Schwartz. (Postgraduate clinic in dermatology and syphilology.) Amphitheater, Mallory Building, Boston City Hospital.

\*12:00 m. Grand rounds. Children's Medical Service, Ether Dome, Massachusetts General Hospital.

##### SATURDAY, JUNE 16

\*10:00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

##### MONDAY, JUNE 18

\*12:00 m.-1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

##### TUESDAY, JUNE 19

\*9:00-10:00 a.m. Medical clinic. Infants' Hospital.

\*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

##### WEDNESDAY, JUNE 20

\*12:00 m. Clinicopathological conference. Children's Hospital.

\*12:00 m.-1:00 p.m. Clinicopathological conference, Cambridge Hospital.

\*Open to the medical profession.

JUNE 11. Boston Dispensary. Notice elsewhere on this page.

JUNE 13. New England Pediatric Society. Notice elsewhere on this page.

JUNE 14-19. American Board of Obstetrics and Gynecology. Page 364, issue of March 22.

JUNE 16. American College of Chest Physicians. Page xvii, issue of May 10.

SEPTEMBER 17. American Public Health Association. Page 752, issue of November 30.

mastoid disease also fell (from 1.38 per cent of all admissions to 0.56 per cent). Especially striking was the reduction of purulent otitis media after myringotomy (from 15.6 per cent admissions in the early period to 4.7 per cent later), but even after spontaneous rupture the number of cases diminished

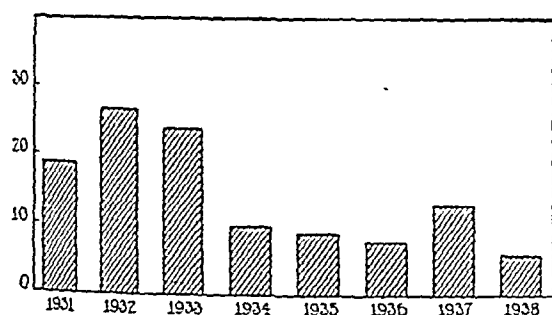


FIGURE 2. *The Incidence of Purulent Otitis Media in Percentage of Admissions. (Bakwin and Jacobziner<sup>14</sup> — reprinted by permission of the publisher.)*

(from 7.6 to 4.5 per cent). This study showed beyond reasonable doubt that it is possible to induce purulent otitis media through excessive manipulation in the ear canal. It is little wonder, then, that there are many who consider the use of the direct otoscope a curse rather than a blessing.

#### DELIVERIES OF BABIES IN HOSPITALS

During recent years there has been a rapid increase in the percentage of hospital deliveries in America. In New York City, for example, 97.3 per cent of all births took place in hospitals during 1943, in comparison with 61.9 per cent in 1929, an increase of over 50 per cent in less than fifteen years.\* The popularity of hospital deliveries has extended to all parts of the country and to rural as well as urban communities.

The hospital obviously offers certain advantages for mother, baby and obstetrician. The arrangements are presumably better, although the occurrence of epidemic diarrhea in some of the best hospitals and its absence from some of the more modest ones should make one cautious about drawing conclusions regarding the value of hospital equipment. Certainly better facilities are at hand for treating emergencies. Furthermore, the modern home — at any rate in many large cities — is often too small to permit the privacy desirable for delivery. For the obstetrician the hospital is a much easier place than the home in which to work.

There are, however, no data indicating that indiscriminate hospitalization for delivery has had a favorable influence on either maternal or neonatal mortality (Fig. 3). Between 1929 and 1933, the percentage of infants born in hospitals in New York

City rose from 61.9 to 78.2 per cent. During the same period the maternal mortality increased from 5.4 to 6.4 per cent and the neonatal mortality showed a slight fall. Since 1933 there has been a steady steep decline in maternal mortality, the rate falling from 6.4 per 1000 live births in 1933 to 2.2 in 1941. During these same years the rate of increase in hospitalization decreased. Whereas the percentage of hospital deliveries rose by 3.2 each year from 1929 to 1933, the annual percentage increase between 1933 and 1941 was only 1.9. The drop in neonatal mortality continued at a slightly accelerated rate.

Of interest in this connection is the experience of the Frontier Nursing Service of Kentucky, organized by Mrs. Mary Breckinridge in 1925. The results of their experience with the first 4000 deliveries are summarized in Table 2.<sup>15</sup> The large majority

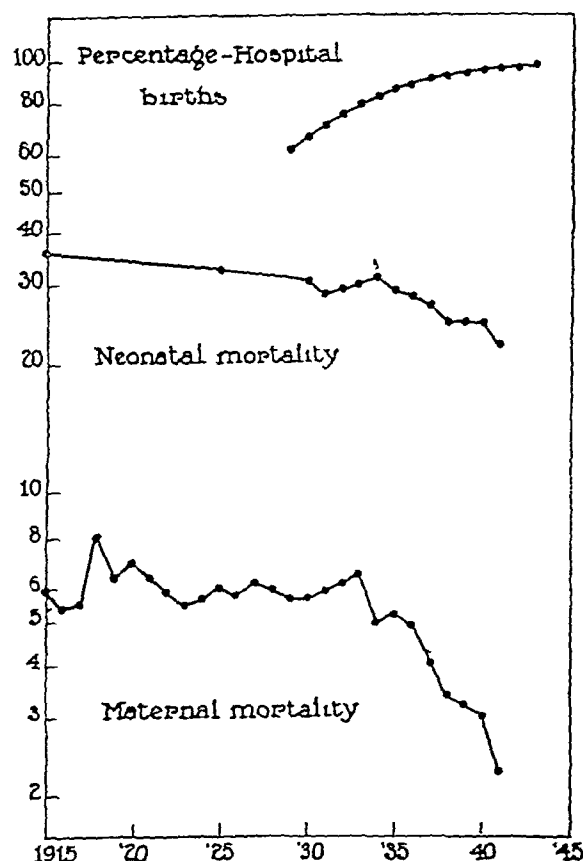


FIGURE 3. *The Percentage of Deliveries in Hospitals, the Neonatal Mortality (under one year) and the Maternal Mortality for New York City (1929-1943).*

(92.7 per cent) of deliveries were done in the homes, which were extremely poor ones, and by midwives. The maternal mortality was only 0.75 per 1000 births, as compared with 5.6 for the white population of the United States at the same time and 5.2 for the white population of Kentucky. Operative

\*These data were kindly supplied by T. J. Duffield, Registrar of Records, New York City.

sicians, who selected 45 per cent of these for tonsillectomy and rejected the rest. The rejected children were re-examined by another group of physicians, who recommended for tonsillectomy 46 per cent of those remaining after the first examination. When the rejected children were examined a third time, a similar percentage was selected for tonsillectomy, so that after three examinations only sixty-five children remained who had not been recommended for tonsillectomy. These subjects were not further examined because the supply of examining physicians ran out. The study showed that there was no correlation whatsoever between the estimate of one physician and that of another regarding the advisability of tonsillectomy, and the authors therefore concluded that the chance of

mate — this means an annual load of sixty-five thousand tonsillectomies, or two hundred each working day. To the cost of medical and hospital care must be added the money spent by social agencies and school nurses in following up children referred for operation. Tonsillectomy is a factor increasing the cost of medical care. Money spent for this operation could be better employed for more useful health measures.

### MYRINGOTOMY

Until the introduction of the sulfonamide drugs it was not unusual for the large majority of infants in a hospital ward to have purulent otitis media during the winter months. The high incidence of myringotomy was by no means limited to hospitals.

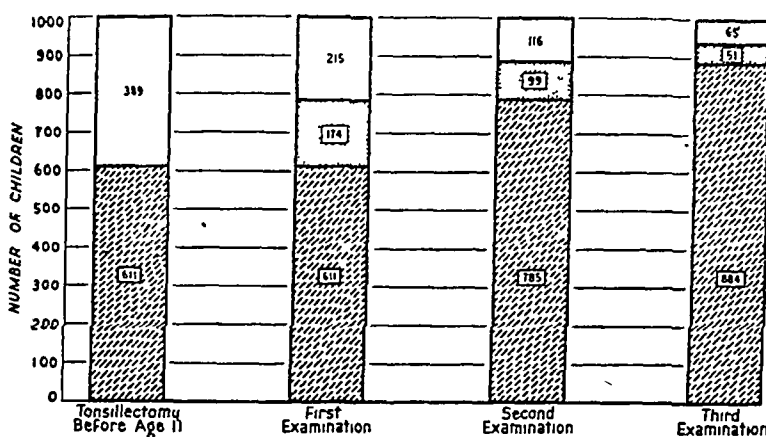


FIGURE 1. *The Theoretical Survival of Tonsils after Medical Examination.*

a child's being recommended for operation depended principally on the physician rather than on the child's health status.

If anyone suspects that financial considerations influenced the judgment of the physicians, the study showed this not to be the case. For of the children who took to a free clinic their school medical examination slips calling attention to their tonsils, practically all were operated on, whereas of those who went to private physicians only a small proportion were operated on.

The American Child Health Association report emphasized that tonsillectomy, as currently practiced, represents in the main a useless expenditure of time, effort and money. Furthermore, the focusing of interest and effort on this operation leads to neglect of defects that are in need of correction. It was found that, even in groups of children who had severe dental caries and visual handicaps for which practically nothing had been done, about 60 per cent had had their tonsils removed.

The annual cost of the operation must be great. If half the children in New York City have their tonsils removed — an extremely conservative esti-

mate — this means an annual load of sixty-five thousand tonsillectomies, or two hundred each working day.

The attitude toward otitis media has changed somewhat since the introduction of the sulfonamide drugs. Interest has diminished to a considerable extent and tension and anxiety have lessened. The great diminution in the incidence of purulent otitis media is generally attributed to the new drugs, but this conclusion is not entirely justified, certainly not in the case of infants. It was possible to show at Bellevue Hospital — before the use of the sulfonamide drugs — that the incidence of purulent otitis media in infants could be greatly reduced simply by limiting otoscopic examinations and by laying down stringent criteria for myringotomy.<sup>14</sup>

During the three-year period 1931–1933, 23.3 per cent of the infants under two years admitted to the Children's Medical Service at Bellevue Hospital developed a purulent discharge from the middle ear (Fig. 2). In the five-year period 1934–1938, after the campaign against indiscriminate myringotomy had begun, the incidence was only 8.9 per cent — that is, a little more than one third the previous rate. The proportion of infants operated on for

discriminate hospitalization increases the cost of medical care without benefiting anyone.

### HOSPITAL CARE OF INFANTS AND YOUNG CHILDREN

For some years it has been recognized that the hospital is unsuited for the care of infants. It seems likely that the high mortality in institutions for the care of healthy infants was due to emotional deprivation.<sup>17</sup> Although many hospitals supply play and other outlets for older children, few make any such provision for infants. Rigid segregation for this age group is still the rule in most of the best infant hospitals. Meticulous care is given to the dietary needs, including vitamin supplements, even when the infant is to remain in the hospital for only a few days, yet no attention is paid to the psychologic needs. Parents are carefully excluded, and the babies are handled by doctors and nurses as little as possible.

There is need for a fuller appreciation of the results of emotional deprivation in hospitalized infants. There should be a suitable program.

Runabouts, too, are in general poorly managed in hospitals from a psychologic viewpoint. Little or no time is spent by the nurses in training the child to eat by himself, to dress himself or to control his bowels and bladder. With these functions aside, the child receives little attention and affection unless he happens to become the ward favorite. Here too the nursing staff needs fuller understanding and an active program.

### ERRORS OF PSYCHOLOGIC MANAGEMENT

Although pediatricians have shown an increasing interest in the psychologic care of the child, they still underestimate its importance or are unwilling to make the effort necessary to inform themselves about it. Consequently the field has been left largely to nonmedical groups whose viewpoint is necessarily limited by lack of understanding of the growing child as a whole. The child is caught between the sentimentality of lay groups and the indifference of the pediatricians.

There is a general impression among pediatricians that consideration of the psychologic attributes is time-consuming. This is true to some extent of the treatment of behavior disorders, but it is not true of the handling of the general run of children. It requires little time to explain to a mother the principles underlying child training and the proper technics to be employed. It does not take long to explain to a mother how a crippled child should be managed psychologically and what the results of mismanagement may be. It requires no extra time for the experienced pediatrician to recognize over-anxiety, overprotection, overauthority and so forth in a parent, and it requires but a few minutes to discuss them.

Aside from the fact that positive contributions can be made in this way to the health and happiness of both parent and child, appreciation of the psychologic attributes adds interest and zest to the work of the pediatrician, whose time is so largely taken up with the care of well children and children with common colds.

Pediatrics of the recent past was dominated to a large extent by a mechanistic viewpoint toward child rearing, and little or no attention was paid to emotional and spiritual needs. In its extreme form this attitude was expressed by Watson<sup>18</sup> (who is not a physician) in his book published in 1928. He wrote: "It is a serious question in my mind whether there should be individual homes for children — or even whether children should know their own parents. There are undoubtedly much more scientific ways of bringing up children which will probably mean finer and happier children." Although pediatricians never overtly endorsed these views, nevertheless many of the accepted practices, such as the rigid attitude toward dietary prescriptions and schedules and the discarding of the cradle and many other devices to please infants, implied tacit acceptance. A whole-ome change has taken place within recent years, and children are now looked on as having emotional and mental attributes as well as physical ones.

Praiseworthy as is this change, certain fallacious views have already gained wide acceptance, principally among child psychologists and educators. The reaction to the over-rigidity of the past has led to a policy of overindulgence. Too much discipline has been replaced by too little. The pendulum has swung from a puritanical negation of the lighter pleasures to hedonism. In an effort to prevent insecurity, which to many is the principal aim of child rearing, children are coddled. This is unfortunate, since discipline is necessary for proper training. There is need for a better balanced viewpoint.

### CHEF OR DIETITIAN

It is unusual nowadays to see a new patient who is not receiving vitamin supplements, yet there is no definite clinical evidence that deficiency diseases are at all widespread among children or that any benefit can be derived from the general use of vitamins, except in the case of vitamins C and D in infancy. Aside from the fact that most of the preparations used are expensive and that their administration is an extra chore and means, to a certain extent, invalidizing the child, a major fallacy is implied in the modern attitude toward diet. It is that appetite cannot be trusted in the selection of a proper diet and that laboratory investigations have progressed to the stage where they can be trusted to make such a selection. Except for limited groups, where deficiency disease is prevalent, this is an un-



deliveries were rare. The stillbirth and neonatal death rates did not differ significantly from those of the country as a whole.

Hospitals are unsuited for the care of the newborn. Physicians and parents who would hesitate

TABLE 2. *Statistical Analysis of the First 4000 Deliveries by the Frontier Nursing Service*

Percentage of babies delivered in the home	92 70
Percentage of babies delivered in the hospital	7 30
Puerperal deaths per 1000 live births	0 76
Cesarean operations per 1000 births	0 18
Forceps deliveries per 1000 births	0 83
Neonatal deaths per 1000 live births	30 3*
Stillbirths per 1000 live births	30 20

\*This figure is slightly below the rate for Kentucky during the same period

to permit an older infant in a hospital ward seem to have no qualms about having newborn babies there, even though obstetric nurseries are generally

failure of many mothers to breast-feed their babies. The pediatrician is generally called in several days after delivery, during which time no effort has been made to initiate breast feeding. Instead, a formula has been prescribed, and this, since it satisfies the appetite, discourages the baby from sucking the breast, thereby removing the stimulus for secretion of milk.

The system of bringing babies to their mothers only at fixed intervals and allowing them to remain for limited periods is hardly conducive to proper breast feeding, especially during the early days of life. At this time the feeding demands of the infant are irregular and frequent.<sup>16</sup> Only later, during the third week of life, does a fairly regular demand rhythm become apparent. It is obviously impossible in a hospital to bring a baby to its mother whenever it cries, and this is one of the drawbacks consequent on hospital delivery. But even in hospitals more freedom could be given than is at present the custom. Since the appearance of epidemics of diarrhea

TABLE 3 *Data on Epidemic Diarrhea of the Newborn in New York City (1934-1943).*

YEAR	NO OF OUTBREAKS	NO OF EXPOSED BABIES	NO OF CASES	MORBIDITY %	NO OF DEATHS	MORTALITY %	CASE FATALITY %
1934	1	386	72	18 0	32	8 3	44 0
1935	7	1,649	205	12 4	96	5 8	46 8
1936	9	1,866	262	14 1	135	7 2	51 5
1937	10	1,181	211	17 9	93	7 9	42 1
1938	9	1,614	121	7 5	52	3 1	42 9
1939	19	2,540	362	14 3	132	5 2	36 5
1940	5	221	73	33 5	22	10 0	30 1
1941	12	609	105	17 2	19	3 1	18 1
1942	13	738	156	21 2	30	4 1	19 2
1943	20	1,765	297	16 9	58	3 3	19 6
Totals	105	12,569	1,864		669		
Averages				14 8		5 3	35 9

more crowded than is the usual infant ward. Fortunately the newborn is resistant to many of the common infections that beset the older infant. The immunity of the newborn is, however, limited, as is evidenced by the frequency with which diarrhea, pneumonia, sepsis and other infections occur among them. These conditions are rare in the home, and the baby kept there is obviously not exposed to nursery epidemics.

The number of deaths from diarrhea of the newborn is not inconsiderable (Table 3). During the ten-year period 1934-1943, 669 infants died of this condition in New York City.

A great drawback in the hospital is the separation of mother and baby. This is unnatural and unphysiologic. Certainly among mammals it is the rule that the young remain in close contact with the mother during early life, snuggling against her.

Whereas the hospital facilitates the work of the obstetrician, it hampers that of the pediatrician, especially in the handling of private patients. The obstetric hospital is in good part responsible for the

in the newborn, this artificial situation has been further intensified, and the nurse is now fortified by department-of-health regulations.

That the hospital is the proper place for the delivery of selected patients where difficulties are anticipated is apparent. But some modification of the present system of indiscriminate hospital delivery is indicated. Relegation of the baby to a nursery is by no means a universal practice. It is the custom in most European hospitals to keep the baby in a crib at the foot of the mother's bed. Having a newborn child in a ward with several other mothers and babies is far from an ideal arrangement, but it may be preferable to ours. There are several other alternatives — a return to home delivery except where there are special reasons for hospital delivery, smaller nurseries or a shorter stay of the mother and baby in the hospital.

The subject is a timely one. With the overcrowding in obstetric hospitals at the present time, it is extremely difficult to give a sick child the attention he requires. Aside from other considerations, in-

under ordinary circumstances it bears no predictable relation to the sugar level in the blood, and for clinical purposes the relation has no significance.

The present reliance on the hospital as the proper place for the delivery of babies is also based on rationalization. The hospital, with its up-to-date equipment and its trained personnel, seems far superior to the humble home and the midwife. So we continue to deliver babies in the hospitals in face of the high maternal mortality and the real risks to the baby.

Another reason why many mistaken practices persist is the indifference of the academic pediatrician to the details of everyday practice. Absorbed in the study of disease mechanisms and their management, he lacks interest in or fails to appreciate the importance of such false practices as indiscriminate tonsillectomy and myringotomy. On the shoulders of the academic pediatrician rests also the responsibility for failure to train the physician to practice properly in the home.

A prominent source of pseudodoxia pediatrica is the tendency to do too much. The physician, eager to justify his function, is rarely content to tell the parent of a child who comes for a health examination that the child has no defects that require correction. He finds flat feet, large tonsils, malocclusion, a heart murmur, a tight prepuce, rickets, undernutrition and poor posture. Most of these are normal variants, but the physician often leads the patient's parents to unnecessary trouble, expense and anxiety by his prescriptions.

The mistaken practices and attitudes that have been listed are not isolated phenomena. They are part and parcel of the practice of medicine today, resting on assumptions that permeate daily routines. They represent, so to speak, the dead wood of medicine, perhaps the necessary obverse of gains in medical experience. It seems almost as though the slow acquisition of knowledge were inevitably accompanied by error. Yet the progress of humane science

requires that the freight of error be lessened steadily if the vessel is to make surer and swifter progress. As Marcel Proust<sup>21</sup> so wisely said:

*For, medicine being a compendium of the successive and contradictory mistakes of medical practitioners, when we summon the wisest of them to our aid, the chances are that we may be relying on a scientific truth the error of which will be recognized in a few years' time. So that to believe in medicine would be the height of folly, if not to believe in it were not greater folly still, for from this mass of errors there have emerged in the course of time many truths*

132 East 71st Street

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warranted assumption. Hear what the poet Ogden Nash<sup>19</sup> has to say about modern eating:

Our daily diet grows odder and odder —  
It's a wise child that knows its fodder.

Within recent years another change in children's eating customs has been advocated. It has been proposed that children eat one or more meals a day at school. The purpose of this is to supply the child with at least one "well-balanced" meal a day. According to Miss Dorothy Thompson,<sup>20</sup> heretofore known as a writer on politics but apparently also an expert on children's eating, such a program, financed of course by the Government, would not only greatly improve the health of the children but would also be more economical than the present one.

The effects of these mistaken teachings are widespread and profound. The food one eats and the manner of eating it have been integral parts of the culture of the home. Around the dinner table the family assembles not only to eat but to discuss family problems, exchange ideas and also give thanks to an unknown giver for favors, small and large. Surely we have been endowed with the sensation of taste for some purpose. Eating should mean roasts, sauces, puddings, pies — not calories, vitamins, minerals. A bit of home cooking is what men travel far to enjoy. The dining table should mean lively discussion and conversation, light or profound. It should be a pleasure, not metabolic wrangling. As between chef and dietitian, I choose the chef without reservation.

\* \* \*

There are numerous other erroneous practices. Such are the unnecessary treatment of physiologic bowing of the legs; the premature use of orthodontia; the diagnosis and treatment of rickets because the ribs flare or the legs are bowed or the head shape is unusual, although rickets is not the cause. Physicians continue to prescribe expensive sugars for babies, although their superiority over ordinary cane sugar has not been demonstrated. Vitamin D is prescribed during the summer months, when it is not necessary.

#### EDUCATION OF THE PEDIATRICIAN

A major error in pediatric education is the failure to prepare students properly for practice in the home. Whether or not by intention, the impression is given that the management of disease in the home requires elaborate and expensive procedures. The student, entering practice after leaving a university hospital, believes that proper management of a child with lobar pneumonia includes a blood-cell count, a throat culture, a chest roentgenogram, a urine examination, perhaps a blood culture, and determination of the sulfadiazine blood level. Since he is not able to have these done, he feels that he is doing slipshod

work and consequently lacks that self-confidence which is so important in his work. He acquires, instead, a feeling of inferiority that interferes with the sense of satisfaction to which he is entitled. The medical student and the intern should know that the various laboratory procedures are used in hospitals primarily for purposes of teaching and study, and that he is exposed to them in the hospital so that he may learn to dispense with them in the home except when there are specific indications.

The medical student, learning his medicine in the impersonal atmosphere of the hospital, fails to comprehend the importance of disease and death to the family group. To him a death is a statistic. He is not taught to understand, nor can he be expected to grasp unaided, the sorrow, the feelings of emptiness, frustration and defeat, the fear and even the terror that overcome the parents of a child, ever so young, who has died. If he is to serve his function properly he needs to comprehend these things, — now, perhaps more than ever, since with so many people lacking the consolation of formal religion he must, in addition to his other functions, often take on the work of the spiritual comforter.

A further error in teaching medical students is the failure to emphasize sufficiently the personal nature of disease. Not disease as an abstraction but people with disease is what needs to be stressed.

#### REASONS FOR ERRORS

Why do we continue to countenance practices that we recognize as false?

One of the most frequent reasons for error is the tendency to accept ideas because they seem reasonable even though they have not been checked by experimentation or proved in practice. About twenty-five years ago it was suggested that vitamin D therapy should be withheld in infants with tetany until calcium salts have been given for a day or two. The reason given was that, if vitamin D is administered immediately, calcium is withdrawn from the circulating fluids and deposited in the rachitic bones and the tetanic manifestations are thereby intensified. Although this idea was based on the flimsiest sort of evidence, — indeed, it was quickly found to be false, — it has nevertheless persisted and can be found in the principal American pediatric texts. It has remained because it is an attractive rationalization. This teaching is not only false; it is dangerous. The quickest and most effective way to bring a tetanic child out of the danger zone is by the prompt administration of a large dose of vitamin D.

Another false idea that has survived for some twenty years because it seems reasonable is that an estimation of the sugar in the spinal fluid is of little value without a simultaneous determination of the blood-sugar level. Although it is true that in diabetes mellitus and hypoglycemic shock, the sugar in the spinal fluid may be significantly altered,

simulate body temperature, at or slightly below which the ointments are used clinically. Three such jars were set up for each ointment. At intervals of six, twelve, twenty-four, forty-eight and ninety-six hours, a 1-cc. sample of the water at a point 1 cm. above the center of the watch crystal was withdrawn and assayed for sulfonamide content. The Bratton-Marshall method of assay was used, employing an accurately calibrated Klett photoelectric colorimeter.

Table 1 shows the constituents of the ten ointment bases. It should be noted that use was made of one series containing 5 per cent sulfathiazole and another containing 5 per cent sulfanilamide.

## RESULTS

The results of these studies are summarized in the accompanying graphs (Fig. 1). Analysis of the

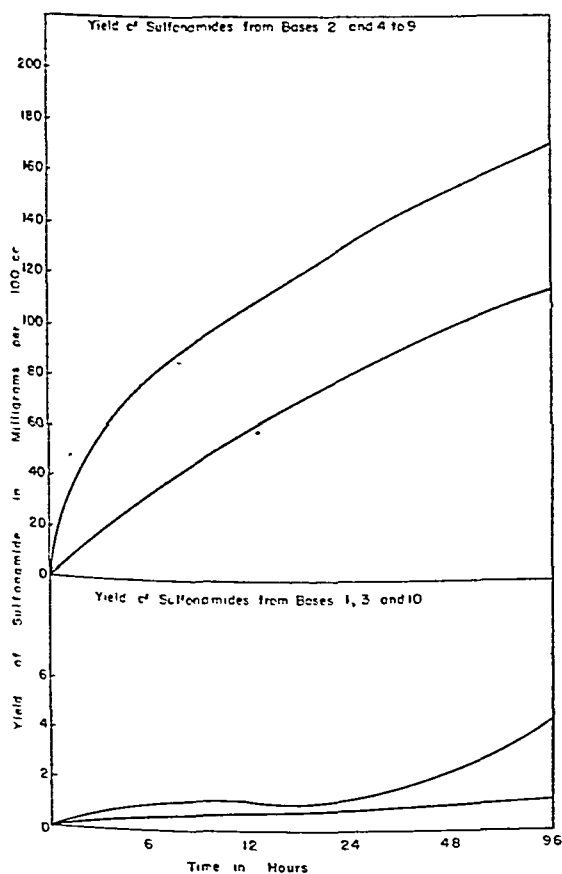


FIGURE 1. Average Yield of Sulfonamides from Oil-in-Water Emulsion and Aqueous Jelly Bases (upper) and from Greasy Bases (lower).

In each graph the upper curve represents the yield of sulfanilamide, and the lower curve that of sulfathiazole. Note that the ordinate scale for the upper graph is one tenth that of the lower graph.

data obtained revealed that the ten bases studied could be divided into two general groups, one comprising Bases 1, 3 and 10, which were found to

yield little sulfonamide to the overlying watery medium, and the other comprising the remaining seven bases, which were found to yield large quantities of sulfonamides to the water. Since the differences in the values for the amount of sulfonamide liberated from the bases within each group did not seem significant, the results at each time interval were averaged for convenience in plotting. Bases 1, 3 and 10, which released little sulfonamide to the fluid in contact with them, are the heavy, greasy type that other investigators<sup>1, 6</sup> also found unsatisfactory as vehicles for applying sulfonamides locally. The amounts of sulfonamide released by these bases were so slight that, in plotting data for this group, the ordinate scale had to be made ten times larger than for the other group of bases so that the curves would be clearly visible. In contrast to the greasy bases, the oil-in-water emulsion bases and aqueous-jelly bases readily liberated large quantities of sulfonamides to the surrounding liquid. The results with the series of bases containing sulfanilamide in general paralleled those with the series containing sulfathiazole, but, as might be expected, the amounts of sulfonamide liberated ran higher for the sulfanilamide series than for the sulfathiazole series, and these differences were much greater for the bases of the oil-in-water emulsion and aqueous-jelly type than for the greasy bases.

## DISCUSSION

Sulfonamides applied locally can be expected to be therapeutically effective only if an adequate concentration of the drugs is maintained in intimate contact with the cutaneous lesion or wound under treatment. When a base so locks the sulfonamides suspended in it that the quantities released to a surrounding aqueous medium are so slight as to be practically negligible, it is extremely doubtful that this requirement will be met. Accordingly, it seems logical to avoid the all-grease or cold-cream type of base for the external application of sulfonamides if optimum therapeutic efficacy is to be realized. Besides obstructing the release of sulfonamides suspended in them, greasy bases have other disadvantages.<sup>7, 8</sup> First, they are not miscible with water or wound exudates. Secondly, it is difficult to bring about an adequate and uniform dispersion of insoluble drugs in bases of this type. Thirdly, their greasiness and stickiness are often objectionable to the patient. Finally, their removal is usually difficult and a frequent cause of pain.

The preparations, such as oil-in-water emulsions and aqueous jellies of the type made up with pectin or bentonite, that were found to liberate larger quantities of sulfonamides to an aqueous medium should, no doubt, be of greater value in local chemotherapy. One characteristic that these preparations have in common is miscibility with water. Hence, they serve to bring the medicaments they contain

## AN EVALUATION OF SULFONAMIDE OINTMENT BASES\*

RUTLEDGE W. HOWARD, M.D.†

BOSTON

THE proved value of the sulfonamides for systemic use has led to a widespread application of these drugs for the treatment of surface infections. Recent studies tend to show that the type of base used as a vehicle for sulfonamides is of great importance. In 1941, Pillsbury and his co-workers<sup>1</sup> showed clinically that sulfathiazole is not so effective in an all-grease base as in an oil-in-water emulsion or stearate vanishing-cream base. In 1942, Gurd, Ackman, Gerrie and Pritchard<sup>2</sup> likewise pointed out that an oil-in-water emulsion base for sulfonamides

ments with a petrolatum base liberate only an inconsequential number of sulfonamides.

The present study was undertaken to evaluate the sulfonamide ointments and creams now usually prescribed from the standpoint of how readily the sulfonamides they contain are released from the base. If the heavy grease or waxy bases so often used in sulfonamide preparations yield little active drug to the tissues being treated, the therapeutic value of such preparations may be expected to be less than desired. Therefore, in choosing a sulfonamide

TABLE 1. *Constituents of Ten Ointment Bases.*

OINTMENT	PERCENTAGE BY WEIGHT	OINTMENT	PERCENTAGE BY WEIGHT
BASE 1. All-grease base: Petrolatum	95	BASE 6. "Washable" oil-in-water base: Water	74
Sulfonamide	5	Glycerin	10
BASE 2. "Washable" jelly base: Water	70.6	Cetyl alcohol	5
Glycerin	18	Stearic acid	5
Pectin	6	Sulfonamide	5
Sulfonamide	5	Amino Glycol (2-amino-2-methyl-1, 3-propanediol)	1
Methyl parahydroxybenzoate	0.2	BASE 7. Bentonite base: Water	85
Sodium bisulfite	0.2	Bentonite (BC Volclay)	10
BASE 3. Wax-oil base: white ointment (U. S. P.): White petrolatum	85	Sulfonamide	5
Sulfonamide	5	BASE 8. Sulfonated hydrogenated castor-oil base: Water	40
White wax	5	Petrolatum	25
Wool fat	5	Diglycol stearate	15
BASE 4. "Washable" oil-in-water base: Mineral oil	64	Sulfonated hydrogenated castor oil	15
Water	23.45	Sulfonamide	5
Beeswax	5	BASE 9. Vanishing-cream base: Water	65
Sulfonamide	5	Stearic acid	15
Triethanolamine	2	Glycerin	10
Methocel	0.3	Sulfonamide	5
Sodium bisulfite	0.2	Tegin-P (propylene glycol mono-stearate)	4.15
Aerosol OT	0.05	Triethanolamine	0.85
BASE 5. "Washable" oil-in-water base: Water	71	BASE 10. U. S. P. cold cream (modified base): Peanut oil	54
Cetosten	15	Water	19
Glycerin	5	White wax	11
Sulfonamide	5	Spermaceti	10.5
Duponol C (principally sodium lauryl sulfate)	2	Sulfonamide	5
White wax	2	Sodium borate	0.5

is more desirable. Diffusion studies by Waud and Ramsay<sup>3</sup> showed that fatty and paraffin bases do not readily yield sulfonamides. They also believe that water-containing bases make the sulfonamide content most readily available. Ackman and Wilson,<sup>4, 5</sup> also in 1942, described an oil-in-water emulsion base for a sulfonamide that, according to their observations, not only ensures constant delivery of the sulfonamide from the emulsion to the wound area but also favors proper drainage. Recently, Cochran<sup>6</sup> has shown that most sulfonamide oint-

preparation for topical application, a physician should consider whether it is likely to maintain the sulfonamide concentration in the tissues at an effective level. This study shows that great differences exist between ointment bases with reference to the amounts of sulfonamide liberated to an aqueous medium.

## METHOD OF STUDY

The method used was as follows. Six grams of each ointment, one sample containing sulfanilamide and the other sulfathiazole, was placed in a glass watchglass so that the ointment presented a smooth, flat surface. Each watchglass was placed in a 6-ounce, covered glass jar containing 100 cc. of distilled water; the jar was then incubated at 37°C. to

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## MEDICAL PROGRESS

### UNDESCENDED TESTICLE\*

WILLIAM C. QUINBY, M.D.†

BOSTON

**D**ISCUSSING the diagnosis and treatment of imperfect descent of the testicle Browne<sup>1</sup> relates an example of the advice given by various physicians to the parents of such a patient. They were told that an immediate operation must be performed if the child was not to be practically a eunuch; that they should wait for five years to see what happened; that the patient should be treated by hormone injections; that operation must on no account be done, since it was invariably unsuccessful; and that the testis was held up by a displaced vertebra that must be treated (this advice was given by an osteopath). On examination Browne found the patient normal.

Of course, such diverse forms of advice emphatically point to a wide lack of unanimity in the minds of practicing physicians, as well as in those of the lay public, regarding the significance of undescended testicle and the importance of its treatment before the onset of puberty. To judge from the indecision frequently found in the past histories of patients coming to a hospital for the relief of undescended testicle, it seems that during the six years that have elapsed since the above incident but small progress has been made toward a unanimous opinion regarding this problem. This is made especially evident in general surgical clinics by the fairly frequent cases of patients well past puberty coming for relief of undescended testicle, toward the correction of which nothing had yet been done because of earlier conflicting or vague medical advice. The statistics of Counseller<sup>2</sup> well illustrate this fact. Of 224 patients studied by him the average age was 19.5 years. Only 20 per cent of these patients were in the first decade of life, and 43 per cent were in the second decade. The rest were even older. It is therefore apparent that the facts that the undescended testicle cannot develop normally because of its faulty position and that correction of this defect in development can be successfully undertaken only at or before puberty are still frequently overlooked. Undoubtedly the pediatrician and the special clinics for children are on the whole well aware of these facts; not so, however, the general family physician.

#### PHYSIOLOGY

The testis is well known to have two functions — that of producing spermatozoa necessary for fer-

tilization, and that of secreting a hormonal substance having an important role of action on the accessory reproductive organs, such as the prostate, the vas deferens and the seminal vesicles. The spermatogenetic function of the testis is not automatic but depends directly on the pituitary gland, the activity of which causes marked stimulation of the testicular cells. In the other direction spermatogenesis is impeded or inhibited by the absence of certain food vitamins, notably vitamin E, and is also unfavorably influenced by heat. It has long been known that the undescended testis (cryptorchid) fails to produce spermatozoa, and by ingenious experimental observations Moore<sup>3</sup> has shown that this depends on the peculiar heat sensitivity of the mammalian generative tissue. The temperature within the abdomen is three to five degrees higher than that within the scrotum, which by virtue of its thin skin, abundant sweat glands and absence of subcutaneous fat acts as a thermoregulator for the testis. Interesting examples of such a mechanism are also furnished by rodents, in whom the testes remain continuously within the abdominal cavity till just before and during the period of rut, at which time they descend into the scrotum. These facts adequately explain the failure of the undescended testis of man to mature and to produce spermatozoa. The second attribute of the testis, that of producing a hormonal substance by the activity of its interstitial tissue (Leydig's cells), is also probably interfered with by the lack of development caused by nondescent of the gland, although in most cases it is not entirely abolished.

A further factor in the problem of nondescent of the testis is found in its relation to the subsequent formation of neoplasms. For several years the opinion has been widely held that the undescended testicle is more prone to the subsequent development of a malignant tumor than is a normal one, and this applies to testicles that have undergone orchiopexy as well as to those that have not been operated on. Statistics concerning this point were either lacking or vague until a recent article by Gilbert,<sup>4</sup> who analyzed 5500 cases of testicular tumor in the literature. In these he found malignancy in 841 cases in which the testis was undescended, and in 63 of these the tumor involved a testicle that had previously been operated on. In 31 of the operated cases, the period between operation and the appearance of the tumor averaged twelve years. Gilbert points out that the 11 per cent incidence of malignant tumor in persons with

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in suspension into close contact with the infected area under treatment; moreover, they can be easily washed off.

Under certain conditions it is desirable to use a preparation having a lubricating effect and in others one having a drying effect. An oil-in-water emulsion provides better lubrication than does a pectin or bentonite jelly, and possesses the additional important advantage that it prevents dressings from sticking. The aqueous jellies tend to dry out rapidly and may prove especially valuable on moist lesions, such as those of impetigo.

The superiority of an oil-in-water emulsion base over an all-grease base as a vehicle for sulfonamides is also demonstrated by the results of agar-plate tests carried out with *Staphylococcus aureus* as the test organism. Figure 2 shows a marked zone of inhibition surrounding a preparation consisting of 5 per cent sulfathiazole suspended in an oil-in-water emulsion base (Base 4). In Figure 3, which shows the results when the same sulfonamide suspended in a petrolatum base (Base 1) is tested, no zone of inhibition is visible. The only apparent explanation for these differences is that the oil-in-water

the all-grease base acts as a barrier, keeping the sulfonamides away from the organisms.

### SUMMARY

Heavy grease and cold-cream bases yield little sulfonamide to an aqueous medium.

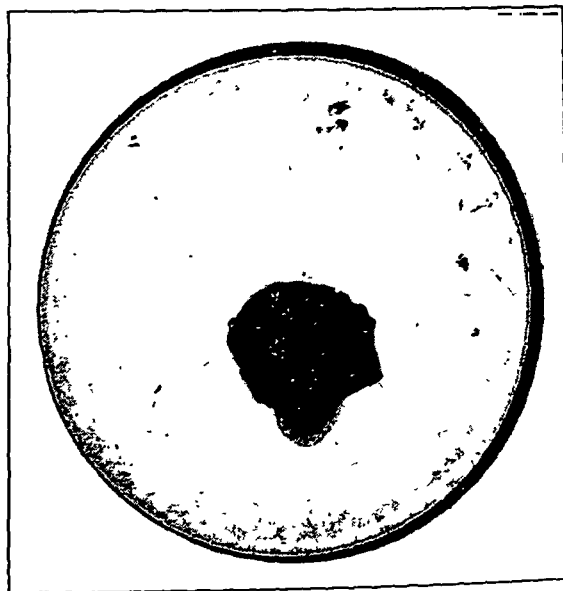


FIGURE 3. Lack of Zone of Inhibition with 5 Per Cent Sulfathiazole in a Petrolatum Base (Base 1).

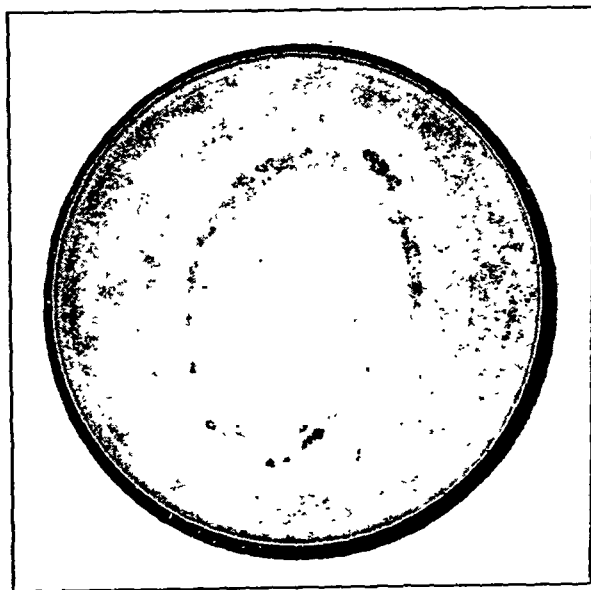


FIGURE 2. The Zone of Inhibition Surrounding 5 Per Cent Sulfathiazole in an Oil-in-Water Emulsion Base (Base 4).

emulsion base readily releases its sulfonamides so that they can exert a bacteriostatic action on the bacteria in the surrounding agar medium, whereas

Oil-in-water emulsion, stearate vanishing-cream, bentonite and pectin-jelly bases yield high levels of sulfonamides to an aqueous medium.

It is apparent that, in prescribing sulfonamides for local use, careful consideration should be given to the choice of a vehicle for the drugs.

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The temperature was 100°F., and the respirations were 35. The blood pressure was 150 systolic, 100 diastolic.

Examination of the blood showed a red-cell count of 4,750,000 and a white-cell count of 17,700, with 56 per cent neutrophils, 15 per cent lymphocytes, 17 per cent monocytes and 11 per cent eosinophils. Toxic leukocytic granules were prominent on the stained smear. The urine gave a green reaction with Benedict's solution but was otherwise negative. An electrocardiogram showed sinus tachycardia at a rate of 120, with a PR interval of 0.16 second. There was a normal axis, with deep S<sub>1</sub> and S<sub>2</sub> and a broad shallow S<sub>3</sub>; QRS was 0.09 second; the T waves were upright, and the ST segments normal.

The patient was treated for congestive failure but soon became unresponsive. His breathing became more shallow, and he expired in respiratory failure approximately twenty hours after admission.

#### DIFFERENTIAL DIAGNOSIS

DR. FRANCIS M. RACKEMANN: I should like to take the last part of this story first and point out that this man died in respiratory failure, which I assume means an increasing respiratory rate, with shallower breathing, and the heart still beating when the end came. That fact, with progressive asthma and the typical chest findings, indicates death from asthma, and I should expect that Dr. Castleman found lungs with pale grayish surfaces and the plugging of the small bronchi. What about the heart? Was there a cor pulmonale? The heart was enlarged, the veins were full, the liver was low, and he had edema of the ankles. He had been treated for congestive failure. On the other hand, the electrocardiogram showed a normal axis. Furthermore, the heart continued to beat; if therefore he did have cor pulmonale, he did not die of it. He could have had a chronic cor pulmonale, and I believe that the right ventricular wall was found dilated and the wall thickened. A diastolic thrill is described. In such cases one can feel with the hand rales of all sorts in the chest, and rales and thrills are easily confused.

This first x-ray film was taken five months before death. It is a lateral view and shows distortion of the spinal column. The lungs are clear, the peribronchial areas are clear, and the diaphragm is low. And that goes along with the idea that he had asthma. I am quite ready to say that he died of asthma, and that he presented the typical findings.

What kind of asthma did he have and what caused it? The onset at the age of twenty means, other things being equal, that it was due fundamentally to allergy. He had been treated with ragweed and mixed *Alternaria* extract. Good physicians would not treat him with these things unless there was clinical evidence that the asthma was worse in the fall of the year than in the ragweed

season. The precise dates are always important in the history of asthma. I should like to speculate and suggest that in this story I can supply the dates even though they are not given in the abstract. I should say that this man probably died in September or early October. This makes the onset one year previously also in September, and that fits the ragweed idea. Five months before entry, when he first came to the Out Patient Department, means April, and so the skin tests were done in May. Treatment was started in July, which is a little late perhaps for best results. I shall say that the asthma was of extrinsic origin and dependent on hypersensitivity to ragweed and molds and possibly to dogs as well.

There are other factors in this picture. From the x-ray films you can see that he had scoliosis, and that means two things to me. He was a long distance runner until a year before he came here. Therefore, he was either not much of a runner or the scoliosis was not too troublesome. I have read somewhere that scoliosis predisposes to tuberculosis, and the fact that he had scoliosis makes one wonder if he had the disease. Against it is this x-ray film of the chest, taken in April. I cannot see the apices. Can you rule out tuberculosis from this film, Dr. Schulz?

DR. SCHULZ: I do not believe that I can rule it out. I can say that there is no evidence of it. The apices are obscured by the deformity.

DR. RACKEMANN: I am going to rule it out anyway, and I am also going to rule out tumor. There is not much reason to think about tumor here.

The second point about scoliosis is that it makes asthma worse, perhaps because the cramping of the chest interferes with the compensatory hypertrophy or emphysema of the lungs. Dyspnea is increased by scoliosis.

There are a number of little bothersome things in the story. In the first place, on the day before death he developed frothy sputum. Asthmatics do not do that often. I do not believe that he died of acute heart failure.

Then, on the day of death he came to the Out Patient Department at 3 a.m. complaining of pain in the abdomen that woke him suddenly from sleep. That was very unusual so far as he was concerned; it was a new thing. Nothing is said about vomiting with the abdominal pain, and he had no fever when he was seen. He was given morphine, which I think would not have been given if it was thought that he had appendicitis. The picture does not sound like appendicitis. It is not like kidney stones. But I think it does sound like mesenteric thrombosis or at least a vascular episode. So please note that. He had a subconjunctival hemorrhage. That also connotes a vascular disturbance. He had some evidence of fluid in the chest and fluid in the abdomen. The numbness in the fingers and arms might have



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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor\**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

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### CASE 31241

#### PRESENTATION OF CASE

A twenty-one-year-old man was admitted to the hospital because of dyspnea.

He had been a long distance runner and in good health until approximately one year before admission, when he began to have a severe cough, which was worse in the early morning and was productive of thick, nonodorous yellow sputum. He noticed wheezing in his chest and became dyspneic after climbing one flight of stairs. The wheezing progressed, and he became dyspneic at rest and when lying down. He was unable to sleep well but obtained no relief from the use of more than one pillow. For several months he had been treated for bronchitis. His cough and dyspnea progressed slowly. He had frequent night sweats and occasional flecks of blood in the sputum.

Five months before admission he came to the medical unit of the Out Patient Department, where loud musical rhonchi were heard throughout both lung fields. Occasional episodes of gallop rhythm and premature beats were heard. The blood pressure was 120 systolic, 98 diastolic. The temperature was normal, the pulse 114, and the respirations 24. An x-ray film of the chest showed marked dorsal scoliosis without evidence of bone pathology. The lungs were clear, and the heart appeared normal. A white-cell count was 17,000. A diagnosis of asthma was made. Four months before admission to the hospital, tests for all common allergens were negative. These tests were repeated two months later,

\*On leave of absence.

at which time strongly positive reactions were obtained to ragweed and mixed *Alternaria* and weakly positive ones to dog hair and *Penicillium*. A program of desensitization against ragweed and *Alternaria* was begun, and the patient felt somewhat better for a week after each injection. One week before admission he developed marked swelling of the ankles, and on the day before entry his sputum became frothy. At 3 a.m. on the day of admission he was awakened by a sharp shooting pain in the low mid-abdomen, which was worse when he changed position. He came at once to the Emergency Ward and obtained prompt relief from morphine. During the morning he became hoarse. He experienced no chills, fever, cyanosis, palpitation or chest pain. His appetite had been poor during recent months.

He had had measles and whooping cough but no other illnesses. The scoliosis was first noticed at the age of eleven without a concomitant illness. His parents and two sisters were living and well.

Physical examination revealed a thin, markedly dyspneic and cyanotic man with a pronounced right dorsal, left cervical and left lumbar scoliosis, with rotation of the vertebral column and winging of the right scapula. The skin was cool and covered with perspiration. There was an area of subconjunctival hemorrhage in the left eye. The pupils were pinpoint and did not react (post-morphine effect). The voice was hoarse and feeble. The neck veins were slightly distended. The heart appeared enlarged to the left and to the right. The rate was 120 and regular, and there was no pulse deficit. A diastolic rumble and thrill were thought to be present over the apex, but auscultation was difficult. Expiration was greatly prolonged. The chest was filled with high-pitched musical rales and coarse crackles on inspiration, with rhonchi, groans and wheezes on expiration. Dullness at the bases and splashing noises on respiration suggested pleural effusion. The abdomen was slightly protuberant, with signs suggesting some fluid; it was tender in the right lower quadrant. The liver was felt four fingerbreadths below the costal margin; it was slightly tender. The spleen was not felt. There was marked edema of the ankles. The femoral pulsations were normal.

## CLINICAL DIAGNOSES

Cor pulmonale, with congestive failure.  
Bronchial asthma.

## DR. RACKEMANN'S DIAGNOSES

Periarteritis nodosa.  
Bronchial asthma, extrinsic.  
Cor pulmonale, chronic.  
Scoliosis.

## ANATOMICAL DIAGNOSES

Periarteritis nodosa, involving especially the heart and lungs.  
Bronchial asthma.  
Cor pulmonale.  
Bronchopneumonia.

## PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy on this young man showed that he did not have fluid in the

all the gross characteristics of miliary tuberculosis, and for that reason we fixed everything in formalin to guard against spreading the bacilli. The heart weighed 280 gm. and was not hypertrophied. The right wall measured 5 mm., indicating definite hypertrophy. The myocardium was pinkish gray throughout, with many soft areas, and we thought that that also was a manifestation of this widespread tuberculous process. Microscopic sections, however, proved that it was not tuberculosis. The histologic preparations showed an unusual lesion.

Each one of the nodules observed grossly in the heart and lungs proved to be a zone of inflammatory and granulomatous reaction in the center of which was a partially destroyed artery (Figs. 1 and 2). The lesions varied considerably, some being very acute and others in their subacute or healing stages. Practically every involved vessel showed partial to complete necrosis of its wall and infiltration with neutrophils, eosinophils, plasma cells and lymphocytes, not only of the wall of the vessel but of a wide zone be-

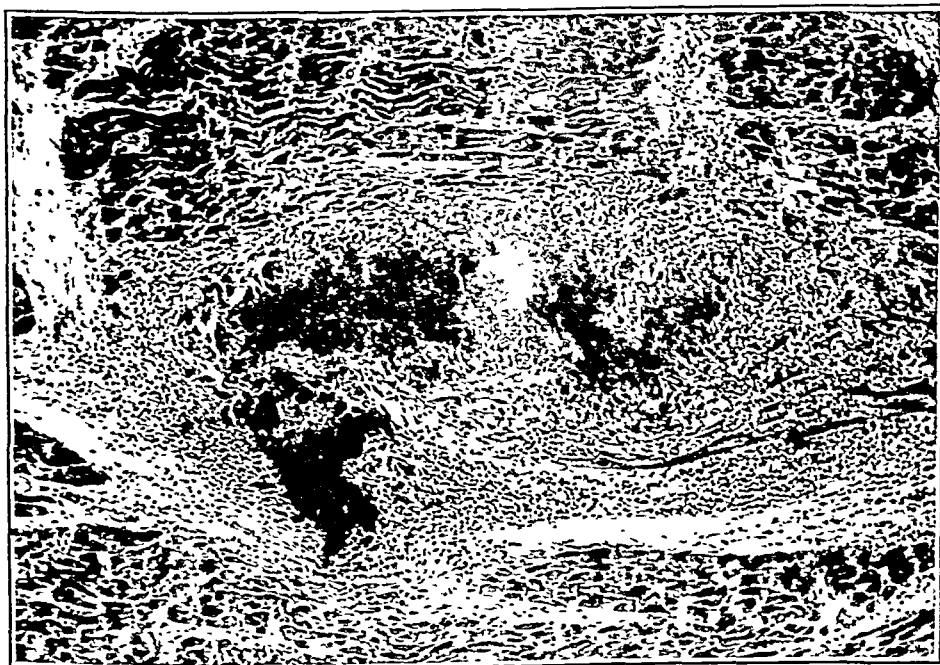


FIGURE 2. Photomicrograph of a Vascular Lesion in the Heart.

chest or in the abdomen. The lungs were covered with small nodules, and scattered throughout both lungs within the parenchyma were similar nodules 4 to 5 mm. in diameter. There were no bronchial plugs to suggest that he died in an asthmatic paroxysm, although I am reasonably sure that he had had asthma. In the pericardium there was about 350 cc. of brownish, somewhat turbid fluid, with a granular exudate over the epicardium. A few small grayish-white nodules were also found over the peritoneum, liver and kidneys. Certainly he had

yond the adventitia. Many of the vessels were thrombosed and in these, especially within the lumen along the destroyed intima, was an extensive granulomatous reaction with numerous foreign-body giant cells. In the heart muscle there was an extensive eosinophilic infiltration not in direct relation to vessels, which possibly represents early infarction resulting from some of the thrombosed arteries. The granulomatous reaction was so prominent that for some time we were considering this case as one of an obscure infection; the almost con-

been due to vascular lesions of the nervous system. All these things put together compel one to consider periarteritis nodosa, in spite of the fact that all the evidence for this diagnosis occurred in the last twenty-four hours. There is one more point — he had a leukocytosis, first noted five months before he died, and again at the end. That one count five months previously was out of place. Why should he have had a count of 17,000 five months before death? The figure is perfectly compatible with periarteritis nodosa, and the 11 per cent eosinophilia also fits in with the idea, although in the fatal cases of periarteritis nodosa observed in this hospital the percentage of eosinophils was much higher. In the

sema and plugs in the bronchi; possibly there were areas of old tuberculosis, and perhaps there was fluid in the pleural and peritoneal cavities, which does not go with the asthma but goes with the periarteritis. Secondly, I believe that he had chronic cor pulmonale that was not fatal, and finally that he had periarteritis nodosa that was probably of five months' duration and that was diagnosable only in the last twenty-four hours. I believe we shall find lesions in the heart and on the pleural surface of the lungs, and I shall throw in the kidneys, even though he did not have red cells in the urine.

DR. J. H. MEANS: I wonder if this man really had fluid in the chest and whether he had a pneumo-



FIGURE 1. Photomicrograph of a Vascular Lesion in the Lung.

eight cases of periarteritis nodosa which Dr. Greene and I\* put together in 1939, all had a leukocytosis of 16,000 or over, and the eosinophils were at least 25 per cent.

From two hundred and twenty-nine references in the literature, however, Dr. Greene found only 19 cases that had asthma and periarteritis at the same time. Of the 19, only 12 had a high eosinophilia. In periarteritis nodosa without asthma, only 15 cases had an eosinophilia. Our patient here had only 11 per cent eosinophils in a white count of 17,000, but evidently that is enough for the diagnosis.

In conclusion, I shall say that this man had asthma, with typical pathology, including emphy-

sema and plugs in the bronchi; possibly there were areas of old tuberculosis, and perhaps there was fluid in the pleural and peritoneal cavities, which does not go with the asthma but goes with the periarteritis. Secondly, I believe that he had chronic cor pulmonale that was not fatal, and finally that he had periarteritis nodosa that was probably of five months' duration and that was diagnosable only in the last twenty-four hours. I believe we shall find lesions in the heart and on the pleural surface of the lungs, and I shall throw in the kidneys, even though he did not have red cells in the urine.

DR. RACKEMANN: I did not have good evidence, it was simply because of the splashing noise and the dullness at the bases.

DR. MEANS: If the splashing was due to effusion in the chest he must have had air in there also, and probably in his stomach.

DR. RACKEMANN: That is correct. I am not too fussy about the point. Whether or not he had fluid would not change my opinion. It is only one of several items.

DR. WYMAN RICHARDSON: I was wondering if the morphine had anything to do with his death.

DR. RACKEMANN: I should say that it had.

\*Rackemann, F. M., and Greene, J. E. Periarteritis nodosa and asthma. *Tr. A. Am. Physicians* 54: 112-118, 1939.

the bones of the pelvis there were scattered nodules of increased density. A gastrointestinal series with the patient in the horizontal position showed the esophagus to be normal. The mucosal folds of the stomach were greatly swollen (Fig. 2). An area of rigidity was seen just below the cardia on the lesser curvature for a length of 8 to 10 cm. On the spot films there seemed to be a shelf at the upper and lower edges of this lesion. A Graham test faintly outlined a normal-appearing gall bladder.

On the eighth day the patient spat up 10 cc. of

became more labored, and without a terminal episode, the patient expired on the twenty-second hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: The story is that of a relatively young man with an acute illness lasting four weeks.

Is it fair to look at the temperature chart? I was quite interested to know whether he had a high plateau type of fever or one that went up and down.

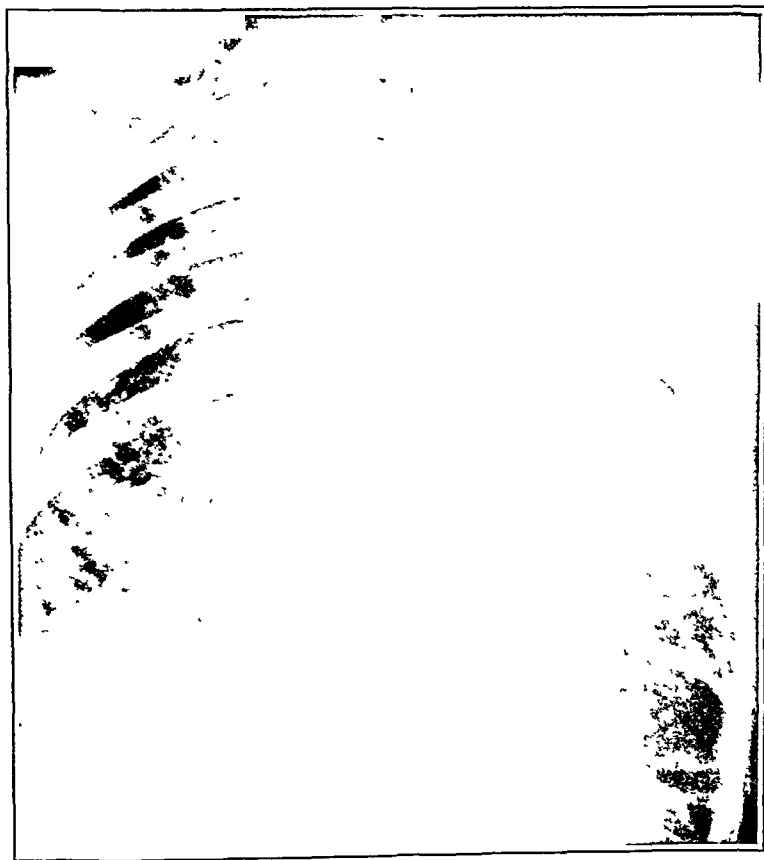


FIGURE 1. Roentgenogram of Chest Showing Extensive Density of an Unusual Pattern.

blood, which he stated came from his nose. A gastric analysis after histamine showed 9.9 units of free acid and 17.5 units of total acid. The sediment contained numerous polymorphonuclear leukocytes and was negative for tubercle bacilli. Repeated stool examinations showed +++ guaiac tests. The hemoglobin was unchanged. Successive differential counts showed the eosinophils to vary from 9 to 24 per cent.

The patient became progressively weaker and more dyspneic. During the third week the temperature rose slowly to 101°F., the pulse to 120, and the respirations to between 40 and 50. The urine and blood were unchanged. The peripheral lymph nodes were thought to be enlarged. Respiration

DR. BENJAMIN CASTLEMAN: You may see it. It is not striking.

DR. RICHARDSON: The fever apparently started off gently and really never did get particularly high. It was not a septic temperature.

First of all I want to run over some of the findings. The primary symptoms were pulmonary, and there was slight hemoptysis early in the disease. I think that this is worth emphasizing. He had night sweats. This is also worth emphasizing. The urine was essentially negative. It contained a few blood cells but no albumin. Several sputum examinations were done; but the story was that of an unproductive cough and there is nothing to suggest that what he was bringing up was really sputum. The alkaline

stant relation of a blood vessel to each lesion, however, justifies a diagnosis of periarteritis nodosa. Similar but less numerous lesions were found in most of the other organs, such as the gall bladder, adrenal glands, liver and kidneys.

It is interesting to speculate about the relation of the asthma and the periarteritis nodosa. We know that it is seen in people who have become allergic to an antigen of some sort. I do not know what could have happened while he had his asthma, but whatever it was it might have started him off on the road to periarteritis nodosa.

DR. CHESTER M. JONES: Had he had any chemotherapy, any sulfonamides?

DR. CASTLEMAN: Not so far as I know.

DR. RACKEMANN: Is it not fair to regard periarteritis nodosa as a pathological picture that occurs in the progress of this disease? When the so-called "toxic factor," whatever that is and however it is concerned with the allergy, reaches a certain point, it produces the peculiar lesions in the blood vessels that we call periarteritis nodosa. I do not believe that the word necessarily means a disease in itself. It is an episode in the course of disease.

## CASE 31242

### PRESENTATION OF CASE

A forty-three-year-old longshoreman was admitted to the hospital because of shortness of breath.

He was well until six weeks before entry, when he first began to note shortness of breath and weakness of the back and legs on climbing stairs and ladders. At about the same time he began to have a dry cough, especially after exertion. He was told that he had bronchitis and was treated with medicines, which afforded no relief. He had had slight hemoptysis on two occasions. Three weeks before admission he became sleepless and orthopneic, requiring three pillows. He had frequent night sweats. A week later he noted pain in his knees and thighs, but no swelling or redness. He also experienced a mild low substernal pain. The dyspnea and weakness had progressed to such a degree that, at the time of admission, he could not dress himself. During the six-week period of illness he had lost 15 pounds; he had had to quit his job two weeks after the onset of his illness.

At the age of four he had scarlet fever. He had not had rheumatic fever or any other severe illness. Four years before the present illness he had submitted to an Army physical examination and had been found to be in excellent health.

Physical examination revealed a slightly pale man with rapid, shallow labored breathing and limited chest expansion. The tongue was dry and red. There was no clubbing of fingers or toes. The neck veins were large but not pulsating. Fine moist rales were heard all over the chest, anteriorly and

posteriorly. No murmurs were heard. The heart was not enlarged. The aortic second sound was equal to the pulmonic. The abdomen showed some voluntary spasm, and the abdominal wall was "sore" from much coughing. Rectal examination revealed a normal prostate. Neurologic examination was negative.

The temperature was 99°F., the pulse 100 and regular, and the respirations 28. The blood pressure was 118 systolic, 75 diastolic.

Examination of the blood showed a red-cell count of 6,100,000, with 17.0 gm. of hemoglobin. The white-cell count was 9700, with 54 per cent neutrophils, 12 per cent lymphocytes, 27 per cent eosinophils, 6 per cent monocytes and 1 per cent basophils. The red cells and platelets appeared normal. The urine specific gravity was 1.030, and the pH 5.2. The sediment contained 3 red cells and 1 to 3 white cells per high-power field, with an occasional hyaline or granular cast. A stool was formed, dark and guaiac negative. Repeated smears of the sputum showed no tubercle bacilli. The serum nonprotein nitrogen was 37 mg. per 100 cc., the calcium 9.0 mg., the phosphorus 3.0 mg., and the cholesterol 205 mg. The protein was 4.98 gm. per 100 cc., with an albumin-globulin ratio of 1.8. The alkaline phosphatase was 16.6 units per 100 cc., and the acid phosphatase 3.3 units. A cephalin flocculation test was negative in forty-eight hours. The carbon dioxide and chloride levels were normal. The blood Hinton test was negative. An electrocardiogram on the first day showed a normal rhythm of 100, a PR interval of 0.17 second, and a flat and diphasic T<sub>1</sub>, an inverted T<sub>2</sub>, a deep S<sub>2</sub> and inverted T waves in CF<sub>1</sub>, CF<sub>2</sub> and CF<sub>3</sub>. At the same time an x-ray film of the chest showed extensive density of a rather unusual pattern in both upper lung fields and in the central portions of the left lower lung field (Fig. 1). The heart did not appear enlarged. The left diaphragm was slightly elevated, and there was mild scoliosis of the thoracic spine.

On the third day marked variation of pulse and heart rate and sounds were noted on expiration. The pulse slowed and weakened during inspiration. A diastolic gallop at the apex and an inconstant diastolic scratchy murmur over the pulmonic area were heard. The respiratory rate rose to 40 for twenty-four hours on the third day, then returned to the former rate of approximately 30. Sputum cultures for streptococci, pneumococci and fungi were negative. The venous pressure and the circulation time were normal. Repeated tuberculin and trichinella skin tests were negative. Re-examination of the chest fluoroscopically and additional films on the fourth day showed no appreciable change in the extensive increased density that involved both lung fields. Further x-ray studies one week after admission showed a normal intravenous pyelogram. A film of the abdomen showed no soft-tissue masses and a normal-sized liver and spleen. Throughout

tumor mass is seen, but there is ulceration of the mucosa along the rigid part of the stomach.

DR. RICHARDSON: I want to play down that lesion.

DR. SCHULZ: These swollen rugae are reminiscent of a case presented at this conference several years ago that proved to be merely gastritis with infiltration of the stomach wall.<sup>1</sup> Lymphoma of the stomach can also have this appearance.

DR. CHESTER M. JONES: Would you be willing to say that this was not an extraluminal gastric lesion, but that it was in the mucosa.

DR. SCHULZ: On the basis of these films I do not believe that one can tell.

DR. RICHARDSON: Now for the diagnosis. If one takes the eosinophilia seriously what does one have to consider? I am not going through all the possibilities, but some of them have to be considered seriously.

I do not know much about Loeffler's syndrome, but it has to do with a pneumonitis and a high eosinophilia. It is relatively acute and benign. I am not up on the literature, but in cases coming from the Mediterranean area I have seen mention of eosinophilia and chronic pneumonitis that lasted for a year or more. I do not believe that any of these cases had an acute fulminating process of this sort. I have seen one patient in this hospital who had an eosinophilia with lesions in the lung, a picture that suggested to me Hodgkin's disease. In the course of a year, however, all the lesions disappeared, as did the eosinophilia, and the patient made a spontaneous recovery. In the present case the disease seems to me to be too widespread and too quickly fatal to consider this group, and therefore I cross them out.

I think that one can make out a good case for periarteritis nodosa, whatever that may be. It is a clinical hodge-podge when one tries to make of it a clear-cut clinical picture. This case does not follow the pattern that one encounters in the asthmatic type. There is no peripheral neuritis, no mesenteric thrombosis, no renal symptoms, and only slight evidence of any actual coronary involvement. Furthermore, I do not believe that we see such a chest picture in the usual type of periarteritis nodosa. It seems to me that the course is too acute for a case of periarteritis nodosa, and in spite of the eosinophilia I am going to throw that diagnosis out. Also, bone lesions would be extremely rare with periarteritis nodosa.

Trichinosis can be fatal. When it is, I believe that it would cause a typhoid-like picture, which this patient did not show. There may be central-nervous-system involvement in fatal cases. Two skin tests were negative. If one is going to pay any attention to such tests it seems to me that they should have been positive in this case. I am going to rule it out.

Tumor seems to me the logical diagnosis in this

case. There is widespread disease involving bone, with lesions that Dr. Schulz says are consistent with metastatic tumor of the bone. There is a lesion in the stomach, and one can logically say that this patient had a tumor of the stomach with widespread metastases, or possibly primary tumor in the lung, with metastases elsewhere. Eosinophilia with tumor involving the lung is sometimes observed. I saw a case not so long ago with eosinophilia due to bone metastases from a pancreatic tumor, but if one is going to suggest tumor as a cause for eosinophilia there should be an accompanying anemia and changes in the blood characteristic of widespread bone-marrow involvement. This man had no anemia, in fact he had a polycythemia, probably due to a certain amount of dehydration and possibly accentuated by some anoxemia, although he is not described as being cyanotic. I do not get the feel from this case that it was a malignant tumor. It was rapidly fatal without any of the really good localizing signs or symptoms that one would expect with a rapidly fatal tumor. It is the kind of death that one might expect from acute leukemia. Nothing suggesting this was observed in the blood smear. Then we have the lymphoma group. It is rare to see a case as quickly fatal as this in any of the lymphomas, unless one includes acute leukemias, which I have already mentioned.

The whole picture to me is that of infection, and whereas I say that tumor is the logical diagnosis, I am going to throw that out also. It may be an infection that I know nothing about or that I have not thought of, in which case there is no use in talking any more. The only infection that I can think of that might produce such an acutely fatal illness is an acute miliary tuberculosis. Does miliary tuberculosis cause eosinophilia? I do not remember having observed it, although I have not seen many cases. That is one point against it. The tuberculin test was negative, but the tuberculin test is frequently negative in overwhelming infection by the tubercle bacillus. So we can allow that. The third point against it is this osteoblastic activity in the bone, which one would think ought to be osteolytic. I am not sure whether tubercles scattered throughout the bone marrow can "tickle up" the osteoblasts enough to lay down a little bone. I do not, however, feel satisfied with the diagnosis of tuberculosis.

The diagnosis of acute bacterial endocarditis ought to be entertained, but again there is no evidence of embolic phenomena, and the bone involvement does not seem to go with it. I am trying to make a soft bed for myself by saying that tumor is the logical diagnosis, but I am going to cross that out and say that this man had a fulminating infection, probably miliary tuberculosis.

DR. J. H. MEANS: Dr. Napier is here, and I have asked him to comment on the eosinophilia.

DR. L. EVERARD NAPIER: My remarks will not bear any relation to this case, but I have been in

phosphatase was elevated, and this suggests bone disease with osteoblastic activity. The murmur in the pulmonary area could possibly have been due to pericarditis, or to pleuritis from the overlying lung, or it may not have been significant at all. Tuberculin tests were negative. Repeated tests with trichinella antigen were also negative. There was pus in the gastric contents, an observation not frequently made, perhaps because it is not looked for. Perhaps we should see the x-ray films at this time.

DR. SCHULZ: Not quite like it, although somewhat approaching it. The findings in this film in association with the increasing dyspnea make one think about lymphatic spread of tumor, especially in view of the areas of increased density evident in the bones.

DR. RICHARDSON: Let us look at the bones.

DR. SCHULZ: There are many round areas of increased density in the pelvis that look like osteoblastic reaction to metastases. Similar bone lesions can be seen in lymphoma.



FIGURE 2 Roentgenogram of Stomach Showing the Swollen Rugal Folds

I am interested in the lesion in the stomach and the appearance of the chest, as well as some of the bone lesions.

DR. MILFORD D. SCHULZ: The films of the chest show extensive, symmetrically distributed mottled and stringy areas of increased density spreading into both lung fields. These go all the way out to the periphery of the lung fields and seem to be most prominent near the lung roots (Fig. 1). It ushers in as possibilities a whole group of lesions that includes lymphatic spread of tumor, fibrosis, miliary tuberculosis, sarcoid and others.

DR. RICHARDSON: You never see an x-ray of the chest like that with periarteritis nodosa, do you?

DR. RICHARDSON: Do you see areas of osteolytic activity?

DR. SCHULZ: I do not believe so. I think that they are osteoblastic.

DR. RICHARDSON: With widespread tuberculosis in the bone is there osteoblastic activity or is it mostly a destructive process?

DR. SCHULZ: I have never seen it look like this.

DR. RICHARDSON: This is, of course, a miliary process.

DR. SCHULZ: The fluoroscopist observed greatly swollen rugal folds. The films of the stomach show an area of rigidity along the lesser curvature, and this is quite constant on the spot films. No actual

Along this curvature we also found a slightly rigid area 2 to 3 cm. long that was only superficially ulcerated. The mucosal folds, however, were prominent (Fig. 4), and this prominence is undoubtedly



FIGURE 5. Photomicrograph Showing Nests of Carcinoma in Distended Lymphatics of the Lung and Pleura.

what was seen in the x-ray and led Dr. Jones to think of a lymphoma, because lymphoma does spread in submucosal tissues and elevates the mucosa. Of course, carcinoma can also spread in that way. These mucosal folds were high and could

not be depressed so that we knew there was something, almost certainly a neoplasm, beneath the mucosa. Microscopically all the lymphatic vessels in the pleura and lungs were plugged with nests of neoplastic cells, which proved to be those of an undifferentiated carcinoma (Fig. 5). The primary lesion was, of course, the rigid area in the stomach; it had extended throughout the submucosa to involve the serosal lymphatic vessels, the peripancratic lymph nodes and the peritoneum. The vertebral bone marrow was grossly involved, and it is surprising that the red-cell count was high. Two or three other counts were taken, and all were in the neighborhood of 5,000,000.

DR. RICHARDSON: If one had looked at the smear I suppose one might have found some evidence of red-cell activity.

DR. CASTLEMAN: This lung picture of lymphatic spread of metastases has been recently described by Dr. Mueller of the X-ray Department and by Dr. Sniffen of this laboratory.<sup>2</sup> About 70 per cent of all cases of lymphatic spread of cancer of the lungs come from the stomach: they usually occur in young persons, and the course is rapidly fatal.

DR. JONES: I think that it cannot be stressed too much that miliary lesions in the lungs may be due to many causes other than tuberculosis. One of the most frequent is metastatic malignancy.

#### REFERENCES

- 1 Case records of the Massachusetts General Hospital (Case 29421). *New Eng. J. Med.* 229:658-660, 1945.
- 2 Mueller, H. P., and Sniffen, R. C. Roentgenologic appearance and pathology of intrapulmonary lymphatic spread of metastatic cancer. *Am. J. Roentgenol.* 53:109-125, 1945.



the tropics, where we see a good deal of eosinophilia, much of which we cannot understand. We call it idiopathic eosinophilia. Frequently we find it running up to 60 or 70 per cent without any obvious



FIGURE 3. Photograph of the Pleural Surface of the Lung.

reason. Another aspect of eosinophilia in the tropics is the high eosinophilic count in the normal population, as compared with the figures one sees in the textbooks that are based on experience in temperate climates. We have taken counts of so-called "healthy people" in India and found an average eosinophilic count of 14 per cent. A good deal of this is attributed to parasitic infestation. That is not the whole story, however. When we exclude infestation we find an average eosinophilic count of 5 to 7 per cent. So the presence of eosinophilia would not excite me the same way that it does you here. The one thing you think of is trichinosis or trichiniasis, — it should really be called "trichineliasis" to be correct, — but we do not think of that in India because we scarcely ever see it. We have seen eosinophilia of the lung or eosinophilic pneumonitis, but it is essentially a benign disease.

DR. JONES: I saw this patient and thought that he probably had a lymphosarcoma originating in the stomach. The chest findings were perfectly consistent with such a diagnosis, and the x-ray film of the stomach showed a curious mucosal pattern, which was like that of several cases of lymphosarcoma of the stomach that I have seen. On the basis of this trabeculation of the gastric mucosa and the rest of the story, that is, the chest findings and the bone lesions, I thought that lymphosarcoma secondary to a primary focus in the stomach was the logical diagnosis.

#### CLINICAL DIAGNOSIS

Lymphosarcomatosis.

#### DR. RICHARDSON'S DIAGNOSIS

Miliary tuberculosis.

#### ANATOMICAL DIAGNOSES

Carcinoma of stomach with metastases to the regional lymph nodes, pleura, lung, pericardium, peritoneum and vertebrae.

Lymphatic spread of pulmonary metastases.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Both lungs were voluminous and filled the entire chest cavity. Scattered over both pleural surfaces was a yellow-white, lacelike network, which reminded me a bit of the lacteals in the intestines when they are ballooned with fat. This network was bright yellow in places and formed a pattern of the entire lymphatic system of the pleura (Fig. 3). It was very striking. This pleural process involved the entire pleura and extended on to the pericardium at the pleural reflection. This same lymphatic engorgement was seen throughout



FIGURE 4. Photograph of the Mucosal Surface of the Stomach.

the parenchyma of both lungs. We, of course, thought of metastatic carcinoma and focused our attention on the stomach. Along the lesser curvature we found enlarged lymph nodes adherent to the pancreas, but the pancreas itself looked normal.

knock-knees and condemn them to orthodontia, forcing them to wear bird cages in their mouths. We believe that, in order to earn our guinea, we should fix something, when often the best service we could perform would be to pocket the fee and leave the patient alone.

## MEDICOLEGAL ABSTRACTS

THIS issue of the *Journal* contains the initial article of a new department, "Medicolegal Abstracts." These abstracts have been and will be prepared by members of the law firm, Palmer, Dodge, Chase and Davis, and it is hoped that a sufficient number will be available so that one can appear monthly.

Many decisions in various courts of law are of vital interest to members of the medical profession and although certain of these are not nationally applicable, being based on the statutes of a single state, they give an idea of the trend of legal thought in matters pertaining to medicine.

These abstracts will be divided into four main groups, each with various headings, as follows: regulation of practice by government (power of government, unauthorized practice, qualification to practice, unlawful operations and treatment, and regulation of professional conduct); relation of patient and physician (right to compensation, liability for malpractice, and authority to operate and to give treatments); testimony by physicians (privileged communications between patient and physician, and medical expert testimony); and institutions (medical societies, medical schools, medical journals, and hospitals).

## OBITUARY

### ABRAHAM RUDY

1895-1945

Abraham Rudy was born in Bialystok, Russia, on February 18, 1895. He studied at the University of Rouen, Moscow University and the University of Berlin, receiving the degree of M.D. from the last-named institution in 1923. In the same year he came to the United States and interned at the Beth Israel Hospital in Boston from 1924 to 1925. During the following year he assisted Dr. Frederick

M. Allen at the Institution for Metabolic Diseases. From 1926 to 1928 he was assistant in medicine at the Mount Sinai Hospital in New York City.

In 1928 he returned to the new Beth Israel Hospital in Boston, where he helped organize the Diabetic Clinic. As head of this clinic he devoted the next seventeen years to assiduous work and constant study. In his quiet, scholarly way he made important contributions to the understanding of the disease to whose alleviation he had devoted himself. He wrote on the role of heredity in diabetes, the carbohydrate metabolism of the skin, vitamin deficiencies in diabetics, diabetic retinitis and the neurologic manifestations of diabetes. He was the author of two books, *Practical Handbook for Diabetic Patients* and *Simplified Diabetic Manual*. His authority was recognized by the New York Diabetes Association, which invited him to write two of the fundamental concepts in *Treatment of Diabetes Mellitus and Its Complications*.

Abraham Rudy was instructor in medicine at Tufts College Medical School and associate in medicine at the Beth Israel Hospital. He was a member of the Massachusetts Medical Society, American Medical Association, Greater Boston Medical Society, Boston Society of Biologists, New England Heart Association, Society of Endocrinology and American Diabetes Association, as well as a fellow of the American College of Physicians.

Doctor Rudy's twenty-odd papers were the result of hard work, keen investigation, enthusiastic inquiry and painstaking clinical investigation. In his contacts with students, colleagues and patients he was invariably gentle, sympathetic and helpful. He had infinite patience. In the last two years of his life, with full knowledge of his fatal illness, he continued his daily work, influencing by precept and example all those who knew him. He was an inspiring physician.

S. S. and H. S.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

SHEEDY — John F. Sheedy, M.D., of Lawrence, died April 2. He was in his seventy-fourth year.

Dr. Sheedy received his degree from Baltimore University School of Medicine in 1898. He was a fellow of the American Medical Association.

WRIGHT — Rebekah Wright, M.D., of Brookline, died March 29. She was in her seventy-third year.

Dr. Wright received her degree from Northwestern University Woman's Medical School, Chicago, in 1896. For many years she was associated with the Massachusetts State Department for Mental Diseases as a consultant in hydrology. Since February 1, 1945, she had been consulting hydrologist at the Connecticut State Hospital, Middletown. She was a member of the American Medical Association, the American Psychiatric Association and the New England Society of Psychiatry.

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## NON NOCERE

THERE come times in the course of human activities when, if we are wise, we pause and look over the lay of the land; see in what direction we are heading, where our goal lies, and if we have been on the right road. It is too easy for us to drift with the crowd, to join an easy-going pilgrimage with no certain knowledge of its shrine and with no critical ideas how the march should be conducted. We are a little like the wartime Londoner who attached himself to the end of a long sidewalk queue and after a while was asked by a passing friend whither he was heading. "I don't know," was the reply, "but it must be pretty good, this queue is so long."

Dr. Harry Bakwin, in his paper "Pseudodoxia Pediatrica," presented before the American Pediatric Society last fall and published elsewhere in this issue of the *Journal*, points out certain false practices into which pediatrics has fallen but from some of which it has recovered.

Midwifery, perhaps even obstetrics rather than pediatrics, has been responsible for the wiping out of the mouths of newly born infants and for the harsh removal of the protective vernix caseosa — practices now largely abandoned. No longer are mineral oil nose drops employed, nor is cod-liver oil poured into the mouths of crying babies, in those circles where the sanctity of human life is still highly regarded. Even the rigid feeding schedule, symbol of Teutonic regimentation and source of parental anxiety and infantile anorexia, is being relaxed in those rarefied strata of society where it is recognized that infants can frequently contribute more to their own training than can their parents.

The indiscriminate tonsillectomy, according to Dr. Bakwin, — physicians, nurses and parents take notice, — may have its ill effects, and this anatomic sunderance, like the joining together in marriage, should not be entered into lightly. Myringotomy is a minor operation not to be performed without due regard to the fact that it is an operation, and it has been shown, even before the use of sulfonamide drugs, that the incidence of purulent otitis media can be sharply reduced by a reasonable abstinence in the use of direct otoscopy.

The lying-in hospital comes into Dr. Bakwin's purview. Convenient it certainly is for the obstetrician, but how safe is it for the infant, that by-product of obstetrics? There are risks to well babies lurking in crowded nurseries, not the least of which is the dreaded epidemic diarrhea of the newborn. In too many cases the pediatrician enters these temples of accouchement on sufferance only, and the obstetrician determines the alimentary career of the little visitor, come hell or high water.

We have, in fact, committed ourselves to a course of too much meddling in the physiologic affairs of our tots of destiny. We assail them with vitamins, regulate their feeding times and the methods of feeding them, correct their flat feet, unbend their

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Trichinosis.* By Sylvester E. Gould, M.D., D.Sc., pathologist and director of laboratories, Eloise Hospital, Eloise, Michigan and assistant professor of pathology, Wayne University College of Medicine, Detroit. 8°, cloth, 356 pp., with 128 illustrations. Springfield, Illinois: Charles C Thomas, 1945. \$5.00.

The incidence of trichinosis in the United States has increased greatly in the past decade. Most of the cases studied after autopsy were not diagnosed during lifetime, revealing that the disease is not usually recognized except when it occurs in epidemic or severe form. The purpose of the volume is to bring the more important aspects of trichinosis to practitioners and possibly also to the attention of those producing and handling pork. An extensive bibliography of 32 pages concludes the work. The book is well printed on good paper and is illustrated sufficiently to bring out special points in the text.

*A Method of Anatomy: Descriptive and deductive.* By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S. (Edin.), professor of anatomy, University of Toronto. Third edition. 4°, cloth, 822 pp., with 729 illustrations. Baltimore: Williams and Wilkins Company, 1944. \$6.00.

The text in this third edition of an authoritative anatomy has been revised, and many parts have been rewritten and rearranged. Fifty-five new illustrations have been added, and sixty-nine old illustrations have been redrawn and relabeled.

*Hack's Chemical Dictionary.* Completely revised and edited by Julius Grant, M.Sc., Ph.D., F.R.I.C. Third edition. 8°, cloth, 925 pp. Philadelphia: Blakiston Company, 1944. \$12.00.

Dr. Julius Grant is responsible for this new edition of an essential reference work. The dictionary has been completely revised and brought up to date in every respect, special care being taken to balance the treatment from the American and British points of view. The dictionary now contains over 57,000 definitions. It is recommended for all libraries and all persons having to do with chemistry.

*Immuno-Catalysis.* By M. G. Sevag, Ph.D., assistant professor of biochemistry in bacteriology, Department of Bacteriology, School of Medicine, University of Pennsylvania, Philadelphia. With a preface by Stuart Mudd, M.D., professor of bacteriology, School of Medicine, University of Pennsylvania, Philadelphia. 8°, cloth, 272 pp., with 19 tables. Springfield, Illinois: Charles C Thomas, 1945. \$4.50.

In the preparation of this monograph more than a thousand publications in English, French and German were consulted for material having a direct bearing on the subject matter. The author was unable to consult the literature in unusual languages, such as Russian, Chinese and so forth, although material pertinent to his subject may have been published in these languages. The work is divided into the following parts: antigens as bio-catalysts; antibody as a specific enzyme inhibitor; anti-enzyme immunity; immunity against bacterial enzymes; and the problem of antibody formation against respiratory enzymes. A bibliography of four hundred and eighty-two items is appended to the text.

*Ventures in Science of a Country Surgeon.* By Arthur E. Hertzler, M.D. 8°, cloth, 304 pp., with 85 illustrations. Halstead, Kansas: Arthur E. Hertzler, 1944. Free.

This collection of essays, principally in the field of surgery, epitomizes the experience of Dr. Hertzler over a period of fifty years in medical practice. Here will be found a summary of his original investigations on the anatomy and physiology of the peritoneum and on the healing of wounds. Two interesting chapters on the writing of books and the building of

a library should interest all librarians, as well as physicians who have literary inclinations. The chapter on visual education describes the author's methods in caring for microscopic slides, photographs and drawings.

*A Bibliography of Aviation Medicine: Supplement.* By Phebe M. Hoff, Ebbe C. Hoff, Ph.D., and John F. Fulton, M.D. Publication No. 9, Historical Library, Yale Medical Library. 4°, cloth, 109 pp. Washington, D.C.: Committee on Aviation Medicine, Division of Medical Sciences, National Research Council, acting for the Committee on Medical Research, Office of Scientific Research and Development, 1944. \$2.50.

This supplement brings up to date the literature of aviation medicine scattered throughout medical journals published during the past two years. A total of 2336 entries has been added to the original 5745 listed in the original bibliography. In the supplement more than two hundred additional journals have been added to the nine hundred cited in the original work. All the periodicals noted in the original or in the supplement have been brought together in one alphabet so that readers will not be obliged to refer back to the appendix of the original work. This book should be in all reference collections, as well as in the libraries of doctors interested in aviation medicine.

*Pep, Pills and Politics: An odyssey of two cities.* By Arthur W. Hopkins, M.D. 8°, cloth, 239 pp., with 23 illustrations. Brattleboro, Vermont: Vermont Printing Company, 1944. \$2.50.

This is an interesting autobiography of a country physician who became a power for good in his community. Dr. Hopkins writes interestingly of his childhood, his college and medical-school days at Dartmouth, his internship and the first years of practice. He concludes his narrative with stories about his later years of practice and his participation in town affairs.

*Combustible Anesthetics in Hospital Operating Rooms.* 8°, paper, 16 pp. Boston: National Fire Protection Association, International, 1944. 20 cents.

This advisory pamphlet embodies the report of the Conference Committee on Operating Room Hazards, which was officially adopted by the National Fire Protection Association in 1944. The first five sections contain the recommended safe practice for the use of combustible anesthetics in hospital operating rooms. The sixth and seventh sections contain recommendations concerning electrical wiring and equipment and on the reduction of electrostatic hazard. This pamphlet should be in the library of the superintendent's office of every hospital.

*Surgery of the Hand.* By Sterling Bunnell, M.D. 4°, cloth, 734 pp., with 597 illustrations. Philadelphia: J. B. Lippincott Company, 1944. \$12.00.

This new book was primarily designed to treat reconstruction but has been expanded to include other aspects of surgery that seemed necessary to complete the work. An effort has been made to keep the work concise and not to overburden it with historical references but merely to express the facts on a working basis. It is profusely illustrated and printed on good paper with a good type but is heavy, as is usual with books made of coated paper.

*Essays in the History of Medicine: Presented to Professor Arturo Castiglioni on the occasion of his seventieth birthday, April 10, 1944.* Edited by Henry E. Sigerist, with the assistance of Genevieve Miller. 4°, paper, 358 pp., with illustrations and frontispiece. Supplement No. 5 to the *Bulletin of the History of Medicine*. Baltimore: Johns Hopkins Press, 1944. \$5.50.

Dr. Castiglioni was honored by twenty-six of his associates and friends who collaborated in writing the essays contained in this memorial volume. The bibliographic chapters of Drs. Fulton, Galdston and Proskauer on Polydorus Vergilius, J. A. F. Ozanam and Hans Sachs, respectively, are of particular interest. Miss Genevieve Miller's paper on an early American marine medicine chest is a welcome contribution to the history of Colonial medicine. The volume is prefaced by an interesting dedicatory letter by Dr. Sigerist, followed by a bibliography of the books and articles written by Dr. Castiglioni, comprising one hundred and sixty-four items.

## MEDICOLEGAL ABSTRACT

### Power of Government: Licensing as chiropractors of persons not qualified to be physicians and surgeons.

The effect of a recent decision of the Texas Court of Criminal Appeals may be that a person is permitted to practice chiropractic in that state only if he has satisfied the educational and other requirements to qualify to practice medicine. The court held that the attempt in the Texas Chiropractic Act to license chiropractic as there defined as a separate science violated the State Constitution.

The Constitution provided:

The Legislature may pass laws describing the qualifications of practitioners of medicine in this State, and to punish persons for mal-practice, *but no preference shall ever be given by law to any schools of medicine* [emphasis supplied]

The act provided:

Chiropractic is defined to be the science of analysing and adjusting the articulations of the human spinal column, and its connecting tissues, without the use of drugs or surgery. Chiropractic shall in no sense be construed or defined as treatment or attempted treatment of patients by use of surgery or medicine.

The court treated chiropractic as defined in the act as a "school of medicine," within the meaning of the Constitution, and held that "the term 'schools of medicine,' as there used, means, and has reference to, the system, means, or method employed, or the schools of thought accepted, by the practitioner."

The court went on to point out how the act gave a preference to the chiropractic school of medicine. The court said that the educational qualifications required for the practice of medicine were decidedly more onerous than those required for the practice of chiropractic and that the subject embraced in the examination given applicants for chiropractic differed from those given applicants to practice medicine. The court further pointed out that the act took away from persons licensed to practice medicine the right to do so by the chiropractic system of the healing art and required that they must first qualify by satisfactorily passing the examination required under the Chiropractic Act.

The court argued that the Chiropractic Act gave a preference to a particular school of medicine, although the Optometry Act and the Dental Act, which were in many respects similar, did not give such a preference. The Optometry Act defined optometry as "the employment of objective or subjective means, without the use of drugs, for the purpose of ascertaining and measuring the powers of vision of the human eye, and fitting lenses or prisms to correct or remedy any defect or abnormal condition of vision." And the act provided, "Nothing herein shall be construed to permit optometrists to treat eyes for any defect whatsoever in any manner, nor to administer nor to prescribe any drug or physical treatment whatsoever, unless such optometrist is a regularly licensed physician or

surgeon under the laws of this state." The Courts said:

Thus the distinction between optometry and chiropractic is apparent. One relates to a particular organ of the body, without treating that organ for disease or disorder. Chiropractic relates to the whole of the body, and authorizes the treatment thereof for diseases or disorders.

Under the Dental Act the business of dentistry was to diagnose, treat, remove stains or concretions from teeth, treat, operate or prescribe, by any means or method, for any disease, pain, injury, deficiency, deformity or physical condition of the human teeth, alveolar process, gums or jaws. And the Court said:

Thus, in his particular field of endeavor, the dentist is restricted to a certain part of the human body. He is not authorized to treat the body generally for a disease or disorder. . . .

The Dental Act bears the same distinguishing features as does the Optometry Act.

The court's decision, being based on a violation of the Texas Constitution, may not have an important bearing in other states, for the court points out that many states are without a provision similar to that in the Texas Constitution that no preference shall ever be given by law to any schools of medicine. Nevertheless, the effect in Texas is to require for the qualification of chiropractors the same standards required for the qualification of physicians and surgeons. — (*Ex parte Halsted*, Texas, 182 S.W. [2d] 479 [1944].)

## CORRESPONDENCE

### SHELTERED WORKSHOP

*To the Editor:* Private physicians may send their patients with arrested tuberculosis who are able to do part-time work to the Sheltered Workshop, 35 Tyler Street, Boston. This shop is sponsored by the Boston Tuberculosis Association. All applicants are examined for admission by Dr. H. Louis Kramer on Mondays at the shop at 4 p.m.

Usually beginners are assigned two hours' work each day. The women are taught sewing, and the men carpentry, by well-educated and experienced teachers. Patients on the two-hour schedule arrive at the shop at 10 a.m. and are given a glass of milk and crackers. The patient then works until noon, when a substantial dinner is served. There is a rest hour from 1 to 2 p.m., after which the patients on a two-hour schedule go to their homes. The hours of work are increased by Dr. Kramer until finally the patient is doing a full day's work.

Guidance toward permanent placement in industry is given by the follow-up worker, who is employed by the Boston Tuberculosis Association. During the fifteen-year period in which the Sheltered Shop has been operating it has been found that 80 per cent of the patients who have received training in it have continued to remain well. The majority of these patients have been referred to the shop from board-of-health clinics and state and private sanatoriums: private physicians, however, might well employ this service for their patients. Further details can be secured by telephoning the Sheltered Workshop (Devonshire 8328).

CLEVELAND FLOYD, M.D., President  
Boston Tuberculosis Association

554 Columbus Avenue  
Boston

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## TERMINAL CARE IN CANCER

### A Study of Two Hundred Patients Attending Boston Clinics

RUTH ABRAMS,\* GERTRUDE JAMESON,† MARY POEHLMAN,‡ AND SYLVIA SNYDER§

BOSTON

**M**EDICAL social workers who daily attempt to cope with the task of arranging for the terminal care of cancer patients have long been concerned with the fact that the combination of limited facilities for the care of chronic cases, hospital policies and human nature makes this an almost insurmountable problem. Because this situation became increasingly difficult, four medical social workers representing as many tumor clinics in Boston met to discuss the nature of the problem, to review the limitations of resources and to discover how they could derive mutual help. An analysis of the situation relative to the medical and nursing provisions in the community seemed timely. The social workers combining in this project represented the Beth Israel Hospital, the Boston Dispensary, the Massachusetts General Hospital and the Palmer Memorial Hospital, a division of the New England Deaconess Hospital. All these institutions are set up primarily for the treatment of acute illness with the exception of the last, which has, in addition, limited facilities for chronic cases.

It was decided to study an unselected sampling of 200 patients known to the tumor clinics of these hospitals who had died of cancer within one calendar year to determine the care received by them and the conditions at home during the period of terminal care. The period selected was an arbitrary one — from November 1, 1941, to October 31, 1942. Fifty cases from each of these clinics were analyzed in relation to age, sex, place of death, length of terminal-care period, living conditions, effect of family finances on plan of care, medical and nursing care provided and the question whether hospital care (general-hospital or chronic or both) would have been acceptable to a greater number if available.

"Terminal care" is an indefinite term used flexibly

by physicians, nurses and social workers. For the purposes of this study, it is taken to apply to that period beginning when the patient is failing and only sedation is being given.

For most patients, this period tends to divide itself naturally into two phases — early terminal and late terminal. During the early terminal phase, the patient may be semiambulatory and able to care for himself and to travel to a clinic or a physician's office for medical supervision. Although unable to work, to be economically self-maintaining or to assume responsibility for household tasks, he can go to the table for meals and has bathroom privileges so that he is not yet a burden to his family. The most obvious problems are environmental. If the patient is a housewife, she must be relieved of household responsibility. If the patient is the wage earner, there may be a need for securing financial assistance if the rest of the family cannot assume the burden of support. Transportation to the clinic may also have to be arranged. It seems natural to assume that there are also emotional reactions. Since the patient can to some extent carry on an active life, the family may not at this point have accepted the medical situation, and the emotional upheaval that may follow has not yet occurred. In the late terminal stage, as the patient's condition gradually becomes worse, requiring more and more attention, — that is, complete bed and nursing care, additional medical supervision or hospitalization, — the family is inevitably forced to the realization that nothing further can be done to halt the patient's decline.

Several elements are involved in providing adequate terminal care. These are the patient's medical and nursing needs, the family's acceptance of the medical situation and what it implies, the family's ability to care for the patient at home — both physically and emotionally — the patient's wishes referable to care at home or elsewhere and existing facilities that are available.

\*Social worker, Tumor Clinic, Massachusetts General Hospital.

†Director of Social Service, New England Deaconess Hospital.

‡Social worker, Tumor Clinic, Boston Dispensary.

§Social worker, Tumor Clinic, Beth Israel Hospital.

*Principles and Practice of Surgery.* By W. Wayne Babcock, M.D., acting consultant, Philadelphia General Hospital. 4<sup>th</sup>, cloth, 1331 pp., with 1141 engravings and 8 colored plates. Philadelphia: Lea and Febiger, 1944. \$12.00.

Dr. Babcock's new text on surgery is the work of thirty-seven collaborators, all of whom, with one exception, are affiliated with Temple University. The work covers practically every method of surgical diagnosis and treatment.

*Ourselves Unborn: An embryologist's essay on man.* By George W. Corner, M.D. 8<sup>th</sup>, cloth, 188 pp., with 18 illustrations. New Haven: Yale University Press, 1944. \$3.00.

This small volume contains the Terry Lectures given at Yale University by Dr. Corner. The first lecture is entitled "The Embryo as Germ and as Archive"; the second, "Prenatal Fate and Foreordination"; and the third, "The Generality and the Particularity of Man."

*Contagious Diseases: A guide for parents.* By W. W. Bauer, M.D., director, Bureau of Health Education, American Medical Association. Second edition. 12<sup>th</sup>, cloth, 188 pp. New York: Alfred A. Knopf, 1944. \$2.50.

The first edition of this popular book appeared in 1934, and this edition embodies the advances in the treatment and diagnosis of the contagious diseases that have taken place in the interim. The text has been thoroughly revised and rewritten and should be of help to parents confronted with this type of disease.

*The Pathology of Internal Diseases.* By William Boyd, M.D., LL.D., F.R.C.P. (Lond.), professor of pathology and bacteriology, University of Toronto. Fourth edition, thoroughly revised. 8<sup>th</sup>, cloth, 857 pp., with 366 illustrations and 8 colored plates. Philadelphia: Lea and Febiger, 1944. \$10.00.

This authoritative text has been thoroughly revised in the light of recent advances in pathology. Much new material has been added, and many sections have been rewritten, especially those covering the etiology of rheumatic fever, calcareous aortic stenosis, the time factor in coronary infarcts, the arterial lesions of hypertension, diffuse arteriolar sclerosis, healed infarcts of the lung, the geography of primary carcinoma of the liver, pyelonephritis, intracranial aneurysms and the pathogenesis of poliomyelitis. Twenty-two new figures and four new colored plates have been added to the text.

*Fractures and Fracture Treatment in Practice.* By Kurt Colsen, M.D., tutor to the Department of Surgery and registrar to the Surgical Firm, University of the Witwatersrand, Johannesburg. Second edition, revised. 8<sup>th</sup>, cloth, 154 pp., with 163 illustrations. Johannesburg: Witwatersrand University Press, 1944. 12 shillings, 6 pence (plus 4 pence postage).

This small manual has been written for students and practitioners, and the text has been revised in keeping with advances in the subject since the first edition was published in 1942.

*Arthritis and Allied Conditions.* By Bernard I. Comroe, M.D., associate in medicine, University of Pennsylvania, and senior ward physician and chief of the Arthritis Clinic, Hospital of the University of Pennsylvania. Third edition, enlarged and thoroughly revised. 8<sup>th</sup>, cloth, 1359 pp., with 329 illustrations. Philadelphia: Lea and Febiger, 1944. \$12.00.

This new edition of a standard work has been enlarged by the addition of thirteen new chapters and more than a hundred new photographs. The work has been thoroughly revised, and extensive changes have been made in the text to bring the subject matter up to date. New chapters have been added on penicillin, psychogenic factors in rheumatic diseases, rheumatic manifestations of tropical diseases, Dupuytren's contracture, effect of climate on arthritis, occupational therapy, and differential diagnosis of rheumatoid arthritis. The chapter on massage has been enlarged, twenty photographs having been added. The sections on orthopedic care, roentgen diagnosis and therapy, and physical therapy have been expanded. Rheumatoid arthritis and degenerative joint disease are discussed in detail. The

etiology and treatment of painful shoulder and bursitis, as well as painful feet and backache, are thoroughly covered. The book has been written for the general practitioner, and emphasis has been placed on treatment.

*Manual of Clinical Mycology.* By Norman F. Conant, Ph.D., assistant professor of bacteriology, Duke University School of Medicine, and mycologist, Duke Hospital; Donald S. Martin, M.D., associate professor of bacteriology and associate in medicine, Duke University School of Medicine; David T. Smith, M.D., professor of bacteriology and associate professor of medicine, Duke University School of Medicine; Roger D. Baker, M.D., associate professor of pathology, in charge of surgical pathology, Duke University School of Medicine; and Jasper L. Callaway, M.D., assistant professor of medicine, in charge of dermatology and syphilology, Duke University School of Medicine. Prepared under the auspices of the Division of Medical Sciences, National Research Council. 12<sup>th</sup>, cloth, 348 pp., with 148 illustrations. Philadelphia and London: W. B. Saunders Company, 1944. \$3.50.

During the past ten years the authors have had the opportunity of studying all types of mycoses. They believe that it is necessary to consider mycotic disease in the differential diagnosis of practically every obscure infection.

*The Biological Basis of Individuality.* By Leo Loeb, M.D. 8<sup>th</sup>, cloth, 711 pp. Springfield, Illinois: Charles C Thomas, 1945. \$10.50.

In this book the attempt has been made to distinguish between two types of individuality: the mosaic, which represents the sum of the particular organ and tissue characteristics, thus determining structure, metabolism and motor and psychical activities, and the type that may be designated as the essential individuality, which is characterized by the presence of a chemical factor. These types of individuality are analyzed regarding their evolution and their biologic and physical manifestations. The work is based on a series of investigations on the transplantation of normal tissues and of tumor tissues that the author and his collaborators have carried out in the course of forty-eight years.

*The Art of Resuscitation.* By Paluel J. Flagg, M.D., visiting anesthetist, Manhattan Eye and Ear Hospital, and consulting anesthetist, St. Vincent's, The Woman's, Sea View, Jamaica, Mount Vernon, Flushing, Mary Immaculate, St. Mary's and Nassau hospitals. 8<sup>th</sup>, cloth, 453 pp., with 176 illustrations. New York: Reinhold Publishing Corporation, 1944. \$5.00.

This monograph on asphyxia and resuscitation is based on the author's twenty-five years of intimate experience with unconscious patients. The work begins with a chapter on history, which is followed by one on the principles of resuscitation and by others on asphyxia as a generic and as a specific problem. A large part is devoted to the discussion of the field of asphyxia and resuscitation, especially in the armed forces, in industry and in public health. Part six is on the co-ordination of gas therapy and includes an interesting table on the signs of death. Part seven discusses the instruction of technicians, asphyxia neonatorum and judicial electrocution. A bibliography of ten pages is appended to the book.

## NOTICES

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 21

##### FRIDAY, JUNE 22

\*9.00-10.00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10.50 a.m. What Not to Do in Dermatology. Dr. Edward La-Freniere. (Postgraduate clinic in dermatology and syphilology) Amphitheater, Mallory Building, Boston City Hospital.

##### SATURDAY, JUNE 23

\*10.00 a.m.-12.00 m. Medical staff rounds. Peter Bent Brigham Hospital.

(Notices continued on page xvii)

of change as each case progressed, attempting to maintain emotional security for the patients in the face of limited resources. In cancer, one of the values in the service of the social worker who has gained the confidence of the patient and his family at the time of diagnosis and initial treatment lies in the fact that they can turn to her at any time as needs develop. Because of this, it is often true that,

admission and holding of patients who are untreatable and in the terminal stage.

One hundred and twenty-five patients stated that they would have accepted placement in a chronic hospital if it had been located near home. During the period of this study the only resources of this type available for immediate admission were chronic hospitals so far distant from Boston that the families

TABLE 1. *Age and Sex of Patients.*

HOSPITAL	SEX		AGE		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-90
	MALE	FEMALE	yr.	yr.									
Boston Dispensary	27	23	0	2	0	2	5	18	14	9	0		
Beth Israel Hospital	21	29	0	0	3	1	8	11	18	9	1		
Massachusetts General Hospital	25	25	1	0	2	4	10	15	9	7	1		
Palmer Memorial Hospital	15	35	0	0	2	5	5	17	11	7	3		
Totals	88	112	1	2	7	12	28	61	52	32	5		
Percentages	44	56	0.5	1.0	3.5	6.0	14.0	30.5	26.0	16.0	2.5		

even when in the terminal stage medical responsibility is transferred outside the hospital, the social responsibility in considerable measure remains continuously with the social worker.

It is of interest to know the place where the patient died (Table 2), but this does not indicate in all cases where he was cared for during the preceding weeks

TABLE 2. *Patients Classified according to Place of Death.*

HOSPITAL	PLACE OF DEATH			OWN HOME
	CHRONIC HOSPITAL	GENERAL HOSPITAL	NURSING HOME	
Boston Dispensary	5	22	2	21
Beth Israel Hospital	7	7	8	28
Massachusetts General Hospital	4	6	22	18
Palmer Memorial Hospital	5	14	7	24
Totals	21	49	39	91
Percentages	10.5	24.5	19.5	45.5

or months of the terminal period; nor does it show where he would have chosen to be could his wishes have been carried out. In the early terminal stage, when the patients were still physically somewhat independent, they usually wished to remain in familiar surroundings where their friends and families were accustomed to see and visit them. In the late terminal stage, however, when they were in bed and almost entirely dependent, they often needed and welcomed a placement where constant nursing care under medical supervision could be provided. It will be seen from Table 2 that of the patients included in this study, 21 died in chronic hospitals, 49 in general hospitals, 39 in nursing homes and 91 at home. But in comparing this table with Table 3, showing the attitude of patients toward hospitalization, one notes that only 31 of the 91 who died at home had wished to remain there throughout the terminal period. According to the figures, 169 patients would have preferred care in a general hospital had one been available. It is well known that hospitals have to discourage or refuse both

and friends of patients could visit them only occasionally, with much cost in time and money. Of the 21 patients who died in these hospitals, 13 were without close ties with family or friends, and therefore felt no objection to entering a hospital at some distance from their place of residence. It was believed that the other 8 entered only because of necessity for care and contrary to their own choice. The 39 who died in nursing homes were in no case more than fifteen miles from their own homes, and usually much nearer. The social workers who knew these patients believe that they would have preferred the security of a nearby general or chronic hospital

TABLE 3. *Attitude of Patients toward Hospitalization.*

HOSPITAL	WILLING TO ENTER CHRONIC HOSPITAL IF NEAR	WILLING TO ENTER CHRONIC HOSPITAL IF DISTANT	WILLING TO ENTER GENERAL HOSPITAL IF AVAILABLE	DESIRIOUS OF STAYING AT HOME
Boston Dispensary	30	2	37	13
Beth Israel Hospital	22	1	45	7
Massachusetts General Hospital	45	4	45	5
Palmer Memorial Hospital	30	6	44	6
Totals	125	13	169	31
Percentages*	62.5	6.5	84.5	15.5

\*Percentages are computed on the basis of the total number of patients studied. Some patients expressed more than one attitude and are therefore included in more than one category.

but seemed satisfied with this type of placement, which in most cases was found to be adequate. All the nursing homes used for the placement of these patients were visited and approved by an agent of the Greater Boston Community Council.

#### PROBLEMS INVOLVED IN HOME CARE

Of the 91 patients who remained at home, all except 8 had supervision from a local private physician or a district physician of the domiciliary-care



In each of these clinics the decision regarding the point at which a plan for terminal care should be worked out with the patient or his family rests with the physician who refers the situation to the medical social worker, with recommendations relating to the type and amount of care needed. Correlating the social situation with the medical recommendation, the social worker attempts to work out with the patient and family a plan that will take into consideration the medical and nursing needs, the adequacy of the home environment and the wishes of the patient and family, as well as the facilities that are available. Since it is difficult to prognosticate in terms of life expectancy and amount of care, several plans may be necessary for the patient as the disease progresses, additional attention is needed or the family situation changes.

The necessity of planning for terminal care carries with it a sense of finality. Families, bewildered, often find it difficult to accept the situation. Even when they understand it, their emotional reactions frequently block their ability to move ahead, so that they resist the making of plans. The suggestion of care elsewhere, particularly in a chronic hospital, stirs up implications and anxieties that they are unprepared to accept. Thus, the first reaction is to keep the patient at home even though the physical strain of caring for him and the emotional strain of watching him fail may precipitate physical and emotional breakdowns in the relatives.

The patient, having been advised to discuss a plan of care with the social worker, usually knows only that he may be ill over a long period of time. Thus, he is not always aware of the implications, and many a patient, not knowing the prognosis, prefers care at home secure among loved ones. As he becomes worse, the security of a medical institution assumes paramount importance and the patient, knowing only that he is ill and needs care, often seeks admission to the hospital where he has previously received treatment. A sick person finds it difficult to accept any interpretation regarding hospital policy or differentiation of general and chronic hospitals. "Doctor, why are you telling me to go to another hospital [or "to a nursing home"] when I am sick and need care?" is a frequent question, and a patient groping and searching for relief of pain feels only that the hospital is withdrawing help.

The available facilities necessarily influence the family's attitude and decision in relation to terminal care. Hospitals for the care of patients with chronic illness have lagged far behind other medical services, and little progress has been made in improving them. Massachusetts is widely known for the excellence of its cancer program in its state-aided clinics for education, consultation, diagnosis and treatment. The Commonwealth appreciates that the problem of terminal care merits humanitarian consideration but at present makes no tangible provision for it.

Available chronic hospitals have such long waiting lists that many patients expire while awaiting admission. The city and state facilities are such that it is frequently impossible to admit patients for bed care, and location makes access for visiting by relatives difficult. At one time the superior facilities of Pondville Hospital were available for these patients, but at present the bed capacity has been reduced and is limited in effect to treatable patients. Although many may feel a sense of stigma attached to chronic hospitals and a sense of futility at the suggestion of admission to one, such hospitals are acceptable to more patients than have actually been admitted.

The problems identified with cancer in turn influence facilities that will be available for care of patients in the terminal stage. Among these are odors associated with some forms of malignancy, incontinence, hematuria, colostomies, frequent changes of dressings and the need for repeated sedation. The proprietors of nursing homes claim that these patients need far more nursing care than do others, both because of their physical condition and because of their extreme fear and anxiety.

In Greater Boston there are approximately two hundred and fifty nursing homes varying greatly in facilities, physical equipment and personnel. Of these, only a small proportion are equipped or are willing to care for extremely sick people. Rates vary from a minimum of \$18 to \$40 and upward weekly, to which must be added the costs of medication and essential medical supervision — rates that to the average family become prohibitive.

With the limitations of hospital resources and of nursing-home care, there is little left for the dying patient except to remain at home and to get along as well as he can. The daily visits of the district nurse hardly meet the need of the patient who is taking opiates by injection for relief of pain. Even in prewar days, it was not possible to secure immediately the services of a physician. Some domiciliary medical service is provided by the Boston Dispensary and Massachusetts Memorial Hospitals for those who cannot afford private medical care, but their volume of work makes frequent visiting impossible.

#### GENERAL CONSIDERATIONS

Of the 200 patients studied, 88 patients were males and 112 were females. The largest age group was that between fifty and sixty, with 61 patients. The youngest patient was seven and the oldest over eighty (Table 1).

The length of terminal care averaged fifteen weeks and ranged from one week to two years. Since the physicians did not feel justified in expressing themselves as to life expectancy, the social workers, given the responsibility of advising with the patients and their families concerning possible plans for care, had to foresee and consider the need

of change as each case progressed, attempting to maintain emotional security for the patients in the face of limited resources. In cancer, one of the values in the service of the social worker who has gained the confidence of the patient and his family at the time of diagnosis and initial treatment lies in the fact that they can turn to her at any time as needs develop. Because of this, it is often true that,

admission and holding of patients who are untreatable and in the terminal stage.

One hundred and twenty-five patients stated that they would have accepted placement in a chronic hospital if it had been located near home. During the period of this study the only resources of this type available for immediate admission were chronic hospitals so far distant from Boston that the families

TABLE 1. *Age and Sex of Patients.*

HOSPITAL	SEX		AGE									
	MALE	FEMALE	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-90	
Boston Dispensary	27	25	0	2	0	2	5	18	14	9	0	
Beth Israel Hospital	21	29	0	0	2	1	8	11	18	9	1	
Massachusetts General Hospital	25	25	1	0	3	4	10	15	9	7	1	
Palmer Memorial Hospital	15	35	0	0	2	5	5	17	11	7	5	
Totals	88	112	1	2	7	12	28	61	52	32	5	
Percentages	44	56	0.5	1.0	3.5	6.0	14.0	30.5	26.0	16.0	2.5	

even when in the terminal stage medical responsibility is transferred outside the hospital, the social responsibility in considerable measure remains continuously with the social worker.

It is of interest to know the place where the patient died (Table 2), but this does not indicate in all cases where he was cared for during the preceding weeks

TABLE 2. *Patients Classified according to Place of Death.*

HOSPITAL	PLACE OF DEATH			OWN HOME
	CHRONIC HOSPITAL	GENERAL HOSPITAL	NURSING HOME	
Boston Dispensary	5	22	2	21
Beth Israel Hospital	7	7	8	28
Massachusetts General Hospital	4	6	22	18
Palmer Memorial Hospital	5	14	7	24
Totals	21	49	39	91
Percentages	10.5	24.5	19.5	45.5

or months of the terminal period; nor does it show where he would have chosen to be could his wishes have been carried out. In the early terminal stage, when the patients were still physically somewhat independent, they usually wished to remain in familiar surroundings where their friends and families were accustomed to see and visit them. In the late terminal stage, however, when they were in bed and almost entirely dependent, they often needed and welcomed a placement where constant nursing care under medical supervision could be provided. It will be seen from Table 2 that of the patients included in this study, 21 died in chronic hospitals, 49 in general hospitals, 39 in nursing homes and 91 at home. But in comparing this table with Table 3, showing the attitude of patients toward hospitalization, one notes that only 31 of the 91 who died at home had wished to remain there throughout the terminal period. According to the figures, 169 patients would have preferred care in a general hospital had one been available. It is well known that hospitals have to discourage or refuse both

and friends of patients could visit them only occasionally, with much cost in time and money. Of the 21 patients who died in these hospitals, 13 were without close ties with family or friends, and therefore felt no objection to entering a hospital at some distance from their place of residence. It was believed that the other 8 entered only because of necessity for care and contrary to their own choice. The 39 who died in nursing homes were in no case more than fifteen miles from their own homes, and usually much nearer. The social workers who knew these patients believe that they would have preferred the security of a nearby general or chronic hospital

TABLE 3. *Attitude of Patients toward Hospitalization.*

HOSPITAL	WILLING TO ENTER CHRONIC HOSPITAL IF NEAR	WILLING TO ENTER CHRONIC HOSPITAL IF DISTANT	WILLING TO ENTER GENERAL HOSPITAL IF AVAILABLE	DESIRIOUS OF STAYING AT HOME
Boston Dispensary	30	2	37	13
Beth Israel Hospital	22	1	45	7
Massachusetts General Hospital	45	4	45	5
Palmer Memorial Hospital	30	6	44	6
Totals	125	13	169	31
Percentages*	62.5	6.5	84.5	15.5

\*Percentages are computed on the basis of the total number of patients studied. Some patients expressed more than one attitude and are therefore included in more than one category.

but seemed satisfied with this type of placement, which in most cases was found to be adequate. All the nursing homes used for the placement of these patients were visited and approved by an agent of the Greater Boston Community Council.

#### PROBLEMS INVOLVED IN HOME CARE

Of the 91 patients who remained at home, all except 8 had supervision from a local private physician or a district physician of the domiciliary-care

services supplied in Boston. These physicians visited only when called, and it was difficult for them to give continuous supervision or even frequent emergency relief. Of the 200 patients studied, 101 received visits at home from private physicians and 19 from physicians of the district services. In considering this proportion it should be borne in mind that whereas only 91 patients died at home, nearly all the total group lived at home during some portion of the terminal-care period.

It was known that 47 of these 91 patients received no other nursing care than that of an unskilled relative or friend. Actually, the care they did receive from their families, many of whom had had no previous experience or training in the care of the sick, evidenced great effort and devotion. Although visiting nurses knew 51 of the patients who remained at home, they attended only occasionally and never more than once a day. Of the trained attendants caring for 19 patients, only a few remained in the home for a twenty-four-hour or even a twelve-hour day. In most cases these nurses came for a limited number of hours daily, thereby leaving the greater part of the day for the family to care for the patient.

#### EFFECT ON FAMILY LIFE

The lack of continuous professional medical and nursing care for the patients who remained at home undoubtedly gave rise to some feeling of insecurity and hardship to both patient and family, but was often overbalanced by the satisfaction of maintaining the unbroken family group with the security of home and the devotion of family. It is thought, however, that in some cases the wearing down of reserves of physical and nervous strength and the undesirable psychologic effect on young or unstable members of the family should be carefully weighed with the desire of the patient and his kin that he remain at home. The demands of the sick person are often paramount, with resulting disruption of normal family life, causing problems among children or even older members of the family group.

#### THE LONE PATIENT

The makeup of the household of these patients was carefully studied before plans were made. One of the most frequently challenging jobs for the medical social worker was planning for the hopelessly sick patient who lived, and had lived for many years, alone. At the time of referral 40 patients, or 20 per cent of the series, were living alone. Many of these had become so accustomed to independence that they found it difficult to join any family group. Usually in considering placement for a patient of this type the worker offered a hospital or nursing home and did not suggest entering a family group. When these patients could not pay for nursing-home care, however, their only actual resource was a chronic hospital distant from such

friends and relatives as they possessed. To return the sick person to his own family from whom he had long been separated, or to the family of kin among whom he had never lived, forced him to give up all the independence he had been able to attain and of which he was usually proud. For the patient who was already living in a family group, the immediate problem of planning was not so great. The lone patient had to face almost immediately his needs for the later period of care, whereas the patient already within a family could remain with it long enough to allow considerable deliberation in planning, with the patient himself a participant in the decision concerning plans.

#### COST OF CARE

Financial status looms large as a determining factor in plans for care. One hundred and seven patients were aided either by fully or partly free care while in hospital or by public or private relief agencies, or both, in securing chronic hospital or nursing-home care. The remaining 93 patients were

TABLE 4. *Number of Patients Rated Full Charges for Ward, Clinic or Nursing-Home Care Compared with the Number Rated Part Pay or Free.*

HOSPITAL	RATED FULL CHARGES	RATED PART PAY OR FREE
Boston Dispensary	19	31
Beth Israel Hospital	23	27
Massachusetts General Hospital	33	17
Palmer Memorial Hospital	18	32
Totals	93	107
Percentages	46.5	53.5

able even during long-continued illness to maintain themselves or to receive aid from families that covered their expenses, including payment for hospital care at ward rates (Table 4).

One hundred and twenty-three patients suffered cessation of income or financial difficulty because of the illness itself (Table 5). Seventy-seven families had sufficient income to provide for the patient. To be sure, it must be borne in mind that the period

TABLE 5. *Effect of Cost of Medical Care on Family Finances.*

HOSPITAL	SERIOUS FINANCIAL DIFFICULTY	NO ADMITTED FINANCIAL DIFFICULTY
Boston Dispensary	31	19
Beth Israel Hospital	22	28
Massachusetts General Hospital	39	11
Palmer Memorial Hospital	51	19
Totals	123	77
Percentages	61.5	38.5

of this study covers a time when there was a definite upsurge in employment and consequently incomes were higher than in the previous decade. The time element is often so long in these cases, however,

that it seems remarkable to find that in so large a number of cases long illness had not completely reduced financial resources.

### HOME CARE

The attitude of the family toward the problem of terminal care of the cancer patient (Table 6) was made the subject of direct inquiry. Here entered

small children or of the noisy social life of other adults. — accessibility of medical care, visits by a supervising physician and services of a visiting nurse were also considered. In each case the reiterated wishes of the patient and family were weighed against the apparent result in terms of human adjustment and relations. Table 7 shows the judgment of the four social workers in summary. indi-

TABLE 6. *Attitude of Families Toward Home Care.*

HOSPITAL	EARLY TERMINAL PERIOD			LATE TERMINAL PERIOD		
	WILLING	NOT WILLING	UNKNOWN	WILLING	NOT WILLING	UNKNOWN
Boston Dispensary	35	10	5	22	23	5
Beth Israel Hospital	44	4	2	10	26	5
Massachusetts General Hospital	44	6	0	44	6	0
Palmer Memorial Hospital	30	20	0	20	30	0
Totals	155	40	7	105	85	10
Percentages	76.5	20	3.5	52.5	42.5	5

a number of factors. The close relation between patient and family was often the controlling element, sweeping away all other considerations. Lack of physical equipment or space sometimes forced a decision. Inability to provide for financial support in some cases became a decisive difficulty. Changes in the patient's need and in the family situation necessitated a change in plan. One hundred and fifty-three of the families were willing to give care in the early stage of the terminal periods, while the patient was still up and about and able to look out for himself. One hundred and five wished to continue to do this in the later stage, when the patient was helpless and required constant care. On the other hand, 40 thought best to have the patient placed outside the home even in the earlier period. In judging the suitability of the home the social

cating as unknown those cases in which the findings were insufficient for basing an opinion on them.

There were unsuitable homes in 62 cases (31 per cent) during the early terminal stage, and in 113 (57 per cent) during the late terminal period. This evidences the need of adequate and acceptable provision for cancer patients beyond that now available.

### CONCLUSIONS

In summary, we believe that the individualization of each patient is of paramount importance. Close family ties, when these exist, should be encouraged by close co-operation between the relatives and the social worker in making plans. Community resources — that is, medical and nursing care, financial aid, housekeeping service and so forth —

TABLE 7. *Suitability of the Patient's Home for Care during the Early and Late Stages of Terminal Care.*

HOSPITAL	EARLY TERMINAL PERIOD			LATE TERMINAL PERIOD		
	ADEQUATE	INADEQUATE	UNKNOWN	ADEQUATE	INADEQUATE	UNKNOWN
Boston Dispensary	27	16	7	21	22	7
Beth Israel Hospital	42	7	1	15	34	3
Massachusetts General Hospital	37	13	0	19	31	0
Palmer Memorial Hospital	24	26	0	24	26	0
Totals	130	62	8	77	113	10
Percentages	65	31	4	38.5	56.5	5

worker took into consideration the size and equipment of the home itself, the kind and amount of service available to the patient, the relations within the group and the effect of the patient's illness on the family group, as well as his own feelings and desires. A room to himself — light, airy and equipped with a comfortable bed — and bathroom facilities were considered essential. Continuous and intelligent care, including preparation of meals, was needed within the home, with sufficient funds to buy both food and necessities for nursing care. A peaceful and serene atmosphere with reasonable quiet, — not too much difficulty in the restraint of

should be used to the fullest extent in making possible home care for at least part of the terminal period when this seems feasible. In each case the needs of the family should also be given consideration.

The following needs are submitted as basic to the carrying through of adequate terminal care for the cancer patient: competent medical supervision uninterrupted throughout the course; good nursing service to supplement the supervision of the physician; the services of a medical social worker continuously available for aid and consultation to the physician, patient and family; chronic-hospital facilities sufficient to meet the need of patients de-

siring hospital care, with location within easy reach of the patients — ideally such a hospital should be closely associated geographically with a hospital having a tumor clinic so as to have available the clinical and laboratory facilities and experience of such an institution.

To accomplish these things means the enlargement of present services and the creation of new chronic

hospital resources, with provision for such service and facilities in large part free or at low cost. It is hoped that such provision can soon be made. Every known resource for diagnosis and early treatment is already available. It is felt with increasing urgency that in this dread disease one should, with consistent excellence of care, see through to termination those patients who cannot be cured.

## THE CARE OF THE PATIENT\*

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**M**Y EXCUSE for presenting a nonscientific paper at this scientific meeting is that I believe that a periodic consideration of this important subject is good for all of us. Among the lectures in my student days that are high lighted, none stand out more sharply than the Peabody Lectures, which were titled "The Care of the Patient." Since everyday practice has demonstrated the great importance of this phase of medical practice, I have often wondered why medical schools allot so little time to its consideration. As I remember it, there were only two or three lectures each year on the subject. I suppose the faculty feels that the art of our profession is learned only through example and practice. Perhaps this is correct, although I sometimes question it when I consider the quality and quantity of the literature on the subject and the time that the leaders of the profession have spent on its consideration.

Medicine as it is practiced today is less conducive to the development of the art than it was in the days before the advent of scientific medicine. In our grandfathers' time the doctor's most potent weapon was his personality and his art. Without the specifics of today, he banked heavily on the self-limited character of the majority of illnesses; and through his art he maintained the patient's morale until Nature had effected the cure. He drove his horse and buggy leisurely from call to call, having time to reflect on the mysteries of man's complex psychic make-up. To keep up with medical knowledge required less time than it does today. He could spend more time with each patient, and he grew to know his patients intimately. He was father confessor as well as healer. Today, with chemotherapy, penicillin, shock treatment, liver extract, insulin and the host of other effective therapies, the disease itself has pushed its way to the center of the stage and the patient as a person tends too often to be neglected. The modern mode of travel requires the driver's complete attention, and reflection on his

patient's personal problems results, at least in a traffic ticket. With the advent of the war, the load on the doctor is immensely increased; his time is precious, and the finer intangible aspects of practice suffer. The medical man in the armed forces falls under the influence of regimentation, and routine procedure is the rule unless the medical officer is thoroughly imbued with the importance of his art. Strangely enough, never before has the community so urgently needed the thoughtful care of the true follower of Hippocrates — he who practices the spirit of the oath as well as its letter. Think a moment of the people who crowd your offices. How few of them need the specifics in your bag and how many of them need your understanding heart! The strain of war with its separations, worries and bewilderments increases many-fold the incidence of functional disorders. Chronic fatigue, functional indigestion, tension headache, neurocirculatory asthenia, the irritable colon and the many forms of depression, to mention only a few, are the disorders that consume more than half your working hours and interrupt your much-needed sleep. Although it is true that this curve of incidence is particularly high during these war years, it will not drop appreciably when peace returns, because other problems will add fuel to the fire, such as the readjustment of the serviceman to civilian life, the reassimilation of the wounded into the community, the ever-increasing pace of our civilization and, most important of all, the growing importance of the problems of geriatrics. It is inevitable that chemotherapy, penicillin and the advances in surgery should swell the ranks of the old-age group of patients, and at no time of life is the need for the practice of the art of medicine so great as in old age. Unfortunately, as senescence advances and the ability to varnish daily living with the veneer of self-control is weakened, man's underlying selfishness and pettiness rise to the surface and he becomes a burden to himself and those about him. The person who grows old gracefully is the exception, although this observation may in part be due to the fact that we, as physicians, are likelier to see that group who

\*Presented to the Newton Hospital Staff on January 22, 1945.

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do a poor job of aging, since those responsible for them turn to us for help with the innumerable symptoms of their charges, the more fortunate group coming to our attention only during acute illnesses.

The growing importance of this whole problem is reflected in the current medical literature. New books are appearing on psychosomatic medicine and geriatrics urging men well established in practice to study the problem and develop a technic of handling it. Some have even proposed the development of a specialty of geriatrics, arguing that soon its importance will outweigh that of pediatrics. Be that as it may, the doctor to whom the practice of the art of his profession is as natural as breathing will find little trouble in solving these growing problems in his own practice.

I have been impressed in observing the students under my care, with a real deficiency in their knowledge of what constitutes the art of medicine. They are imbued with a hot devotion to the science of their profession, showing keen interest in the technic of diagnosis, with special emphasis on laboratory and other technical aids, but when questioned about the social history of the patient or the minute details of treatment on which the practice of the care of the patient so often depends, they answer in generalities that indicate a lack of an appreciation of the importance of such knowledge. Their feeling doubtless is that this is the province of the Social Service Department. They will find that when they leave the security of the walls of the hospital or of the Army they will have to be their own social service department or else be content with a meager practice — that is, if there is any degree of competition when they arrive at that golden day.

Unfortunately today, because of the shortage of physicians, the public is willing to put up with treatment minus the art as they put up with mediocre services at every turn. The doctor does not have to sell himself to his patients as he did — to be sure, usually unconsciously — in the past. It has been said that any doctor can build up a large practice if he possesses a good bedside manner, but that does not indicate how badly he practices it. This temporary upset in the balance of supply and demand removes one incentive toward the study and practice of the care of the patient, and the fact that most medical-school graduates are going into the armed forces removes another, at least in the minds of many. Too many fourth-year students believe erroneously that military medicine is cold and efficient and spurns any thought of the finer sensibilities with which the art of medicine is concerned. I have had occasion to talk to wounded men of the Marine Corps who have returned from the South Pacific, and their glowing tribute to the medical officers who treated them stressed the humaneness with which they were handled even above the technical skill which was used. As one of them

stated, "He was my best friend — and I mean friend, not doctor." The need for the art of medicine is universal.

One other obstacle is that it takes more time and energy to practice this kind of medicine. Osler has said the man most to be pitied is the forty-call-a-day man. It is well-nigh humanly impossible adequately to care for the patient on that schedule. Corners must be cut to get through the day, and the more difficult features of practice — those relating to the understanding of the patient as a person — suffer. Such a man easily sinks to the level of a pill dispenser or at best a mere diagnostician. Even the man with a less crowded day avoids the exacting demands of the care of his patients. The best of us are fundamentally lazy, as someone has said, and we try to avoid that which taxes our time and maximum ingenuity. It is easier to get in and get out of the sickroom quickly, dodging the endless questions, the answers to which constitute in part the adequate care of the patient. It is, however, true that there are some patients, especially those in the lonely, psychoneurotic group whose stereotyped questions waste the doctor's time, their solution adding nothing to the real care of the patient except as it acts as a pleasant interlude in the boring hours of the sickroom. It takes a real artist to handle such patients satisfactorily. Osler is said to have been a master in like situations. He would come breezing into the sickroom with a cheery greeting, size up the patient's real needs quickly, and then proceed to divert his or her attention from the unimportant complaints and grumblings by an apt anecdote and leave with specific instructions to the nurse or family, having wasted little time but having effectively instituted therapy necessary for the care of the patient. The long list of carefully written out questions were unanswered, but somehow the patient's mind was at rest and he was satisfied.

I need not argue the crying need of the patient's care, especially today, any further. It may, however, be worth while to consider briefly how the recent medical graduate can go about acquiring the nearly automatic technic that spells success in this care. I certainly cannot set myself up as an authority in this field. I am too young in practice, and the art grows slowly and too often never. I can only refer the neophyte to the literature and urge him to aim at the goal that the many masters in the art have set in the past.

In the first place, it is wise for him to be a student of man himself. This he may do by reading about, observing and talking with his fellow man. Provocative books such as Alexis Carrel's *Man the Unknown*, Fosdick's *On Being a Real Person* and Zinsser's *As I Remember Him* are helpful. An interest, limited as it may be, in his community life demonstrates how the men outside the profession think, talk and live. A close nonmedical friend or

two will serve as a stimulant to argument, especially in front of an open fire, and will help crystallize ideas previously shrouded in foggy generalities. A study of religion will help the neophyte to understand that vital force which is so important in many lives.

In the second place, he should acquaint himself with the literature of those men who have pondered the subject, notably William Osler, Francis W. Peabody, L. Eugene Emerson and Alexander Gibson. I know of no man of medicine who had a fuller, busier life than Osler, yet all his biographers agree that he never lost the human touch. His patient, as a person, always came first in importance before diagnosis, treatment and case discussion. At one time he was walking through the operating room of a Philadelphia hospital when an old man, a pauper, was about to have an ingrowing nail cut out. The old man was frightened nearly to death. When Osler grasped the situation he amazed the students by his rage when he said: "Don't you dare touch that old man. You can do him no good, and you know it. Take him back to the ward."

Osler was constantly reminding his students that the patient is not a piece of experimental laboratory apparatus. He once said: "The practice of medicine is an art, based on science. . . . It has not reached, perhaps never will, the dignity of a complete science with exact laws like astronomy and engineering." A letter written when he was only twenty-five to the father of a young Englishman dying of smallpox under his care in Canada is a masterful illustration of his understanding of human beings. The letter follows:

My dear Sir:

No doubt before this, the sorrowful intelligence of your son's death has reached you, and now when the first shock has perhaps to a slight extent passed away, some further particulars of his illness may be satisfactory. On the evening of Thursday the 22nd and on the following day I discovered unmistakable evidence of the nature of the disease. On Saturday in consultation with Dr. Howard, the leading practitioner of the city, his removal to the smallpox hospital was decided upon. I secured a private ward and took him there in the evening. Even at this date was seen the serious nature of the case and I sent for Mr. Wood at his request. At 10 p.m. I found him with your son, and we left him tolerably comfortable for the night. He was easier Sunday morning, but well aware of his dangerous state. He spoke to me of his home and his mother and asked me to read the 43d Chapter of Isaiah, which she had marked in his Bible. I spent the greater part of the evening talking and reading with him. Mr. Wood called in three or four times in the day and at 9:30 p.m. I found him there again. Mr. Norman had also been in just previously. He was still sensible and requested to see Dr. Howard again in consultation with Dr. Simpson, the attending physician in the smallpox hospital. After 11 o'clock he began to sink rapidly and asked me not to leave him. He did not speak much but turned round at intervals to see if I were still by him. About 12 o'clock I heard him muttering some prayers but could not catch distinctly what they were—"God the Father, Son and Spirit." Shortly after this he turned round and held out his hand, which I took, and he said quite plainly, "Oh, thanks!" These were the last words the poor fellow spoke. From 12:30 he was unconscious, and at 1:25 passed away without a groan or a struggle. As the son of a clergyman and knowing well what it is to be a "stranger in a strange

land," I performed the last office of Christian friendliness I could and read the commendatory prayers at his departure.

Such, my dear Sir, as briefly as I can give them are the facts relating to your son's death.

The little book, *Doctor and Patient*, by Francis W. Peabody,<sup>2</sup> director of the Thorndike Memorial Laboratory at the Boston City Hospital from 1921 to 1927, is filled with good advice on the subject we are discussing. The following quotation is a practical illustration taken from this book.

Suppose, for instance, you find conclusive evidence that his [the patient's] symptoms are due to organic disease: say, to a gastric ulcer. As soon as you face the problem of laying out his regimen you find that it is one thing to write an examination paper on the treatment of gastric ulcer and quite another thing to treat John Smith, who happens to have a gastric ulcer. You want to begin by giving him rest in bed and a special diet for eight weeks. Rest means both nervous and physical rest. Can he get it best at home or in the hospital? What are the conditions at home? If you keep him in the hospital, it is probably good for him to see certain people, and bad for him to see others. He has business problems that must be considered. What kind of compromise can you make on them? How about the financial implications of eight weeks in bed followed by a period of convalescence? Is it, on the whole, wiser to try a strict regimen for a shorter period, and, if he does not improve, take up the question of operation sooner than is in general advisable? These and many similar problems arise in the course of the treatment of almost every patient, and they have to be looked at, not from the abstract point of view of the treatment of the disease, but from the concrete point of view of the care of the individual.

Peabody stresses among other things the great lasting harm that can be done a patient by a careless snap diagnosis of a serious condition that later proves to be incorrect. This is especially true of the diagnosis of heart disease. To tell a man that he has heart disease and at the same time caution him "not to worry about it" is playing with dynamite. Every day the patient looks at the obituary pages and sees mention of men in the prime of life dying suddenly of coronary thrombosis. He cannot appreciate the fact that the prognosis in neurocirculatory asthenia or other functional cardiac disorder is quite different from that in coronary-artery disease. Heart disease is a black label to him. Twenty minutes of careful explanation with this man may mean the avoidance of years of invalidism, at least psychologic if not actual physical invalidism.

Not long ago a young patient of mine got up late, rushed through his breakfast, ran a mile for his train and, while riding into town, experienced palpitation, sweating, weakness and slight pain in the left elbow. When he arrived at work a physician was called who listened to his story, listened to his heart, told him that he had had a heart attack and sent him home by taxi. He had never seen the patient before. He failed to find out that he had had a similar attack ten years previously while playing tennis after a heavy meal, that he had not had the slightest suspicion of anginal symptoms since then, in spite of the fact that he was a strenuous tennis player, skier and bowler, and that he had lost

sleep for the last three weeks because his wife was in the hospital and the household duties had fallen on him. The physician did not even take the patient's blood pressure. If he suspected a coronary attack,—although the history was much more suggestive of paroxysmal tachycardia,—he should, if he had the care of his patient as his first consideration, have suggested further observation, reassurance and an electrocardiogram. When all the evidence had been collected a sane, intelligent talk would have saved years of worry and fear. Now, in spite of a negative electrocardiogram, excellent coronary reserve and a disappearance of all symptoms, it is likely that the words "heart attack" may haunt this patient for years to come. About a year ago the same physician treated an eighty-year-old patient of mine in an institution for the aged for an ulcer of the face for a month in spite of the development of a pearly border. He probably thought that she did not have long to live anyhow, but following x-ray treatment the lesion healed, and she may still have several years of living in comfort. In neither case did this physician consider the mental health and happiness of his patient.

Too much laboratory investigation and prolonged hospitalization are often not in the best interests of the patient. In the anxious patient with a functional disease, they make him suspect that the doctor is unable to locate the trouble and that it must therefore be serious and deep-seated. In the older patient, the laboratory investigations use up the patient's strength and deplete his pocketbook. At best they only satisfy the ultimate scientific curiosity of the doctor and seldom add information that improves the quality of treatment. The best interests of the patient are usually served by a rapid thorough workup, including only definitely indicated laboratory studies. For example, what is the need of a urea-clearance test, phenolsulfonephthalein test and even a nonprotein nitrogen determination if an eighty-year-old patient has a specific gravity in the urine of 1.020 without appreciable albumin or formed elements in the sediment?

There is also the danger of meddlesome medicine. Withholding from the old patient his few comforts such as tobacco, alcohol, coffee and certain items of diet just because this is theoretically sound from the point of view of the disease may at best add only a few weeks of unhappy life. Alfred Worcester<sup>3</sup> has

emphasized this point in his excellent book, *The Care of the Aged, the Dying and the Dead*. We must also question carefully the heroic use of chemotherapy, penicillin and oxygen in trying to close the door to that friend of the aged Osler has spoken of, pneumonia.

Finally, the student who sincerely wants to perfect his technic in the care of the patient will find numerous examples exhibited by the older men in the profession. One of the great advantages of the old preceptor method of medical education was the close association of teacher and student. The latter acquired the fine art of medicine by example, a method of learning that is not readily available from the lecture platform and at bedside teaching rounds. The best teachers, however, exhibit it even in the largest clinics. As always in education, one learns that to which one's senses are attuned and open.

In general our ranks are made up too largely of men overbalanced at one end of the scale or the other. At one end are mostly the younger men stressing the science of medicine and bewildered by the details of the practical handling of the patient. At the other end are the busy older practitioners who in lieu of ready knowledge of the newer therapies and intricacies of diagnosis lean heavily on their knowledge of the patient as a person, giving comfort but missing the satisfactions that come with the thorough understanding of the disease process. The medical student's goal should be a proper balancing of these two cornerstones of medical practice. The relatively rare men who have achieved this goal are the envy of their brother physicians and form the backbone of the profession.

I have tried in this short paper to plead once more for the patient as an individual. For most of you such a plea is superfluous, but if a few of the younger graduates have been stirred into a renewed interest in this important subject, I shall not feel that your time or mine has been wasted. As Peabody<sup>2</sup> stated, "The secret of the care of the patient is in caring for the patient."

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## MEDICAL PROGRESS

### SKIN TESTS IN BACTERIAL AND VIRAL DISEASES\*

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**I**N RECENT years the clinician has employed the products of a variety of bacteria, viruses, protozoa and fungi as antigens in performing skin tests to demonstrate a previous infection with a given pathogenic agent. In numerous cases these tests have proved to be of great value in the differential diagnosis of many infectious diseases, and have been of inestimable aid in determining susceptibility to or immunity against a given infectious agent. In addition, a skin test has been employed to give valuable prognostic information as well as to guide serum therapy in pneumococcal pneumonia. It is the purpose of this paper to review critically certain dermal tests employed in bacterial and viral diseases and to define their usefulness to the clinician. No attempt will be made to discuss the lesser known skin tests, such as the Mallein reaction for glanders. The fundamental mechanism that governs skin reactions in general will be briefly reviewed as a background for the proper understanding of such tests and as a guide to their interpretation.

#### HISTORICAL BACKGROUND

Nearly one hundred and fifty years ago Jenner<sup>1</sup> clearly recorded that persons who had been vaccinated or who had undergone a smallpox infection reacted locally to the inoculation of cowpox with a more rapid reaction than did those who had no previous contact with the virus. This observation was disregarded until one hundred years later, when Koch<sup>2, 3</sup> published his observations on the changed dermal sensitivity following tuberculous infections. The tuberculin test was a direct result of this study.

In 1907, von Pirquet<sup>4</sup> reinvestigated the problem of vaccinal hypersensitivity and suggested that the term "allergy"—that is, altered reactivity—be used to express the changed reaction capacity of the body resulting from infection or contact with a foreign protein. On the basis of this study and a previous one on serum sickness, von Pirquet tried to explain certain clinical features of other infections on an allergic basis. It was an obvious step in the study of these infections to apply dead bacteria or their products to a scarified area of the skin by the same technic as was used for the vaccine virus. As a result, the von Pirquet technic for applying tuberculin was devised. This simple and safe cutaneous

test stimulated efforts to demonstrate allergy in other infectious diseases, as a result of which a number of valuable skin tests have been developed.

#### FUNDAMENTAL MECHANISMS GOVERNING SKIN REACTIONS

It became manifest from the start that there are two distinct types of dermal hypersensitivity. One type corresponds to protein anaphylaxis and can be produced by the injection of any protein, bacterial or otherwise. In this type, circulating antibodies can be demonstrated. The intradermal injection of the test substance results in its union with its specific antibody at the site of inoculation. Such an antigen-antibody combination may be irritating and lead to a histamine-like reaction. Approximately fifteen minutes after injection a wheal with a zone of erythema appears, which usually disappears in a few hours. In the interpretation of this type of reaction it is important to keep in mind that the antigen is a bland substance and produces dermal irritation only after union with its antibody.

The second type of hypersensitivity is a true tissue allergy in which no circulating antibodies can be demonstrated. This type of sensitivity can be established experimentally only as a result of infection or the injection of whole dead bacteria. The dermal reaction so produced is always of the delayed type and leads to a more profound injury of the tissues. There is no reaction for a number of hours following injection; then induration, pain and redness occur, reaching a maximum intensity only after twenty-four to forty-eight hours. In the more intense reactions a central area of necrosis may be present. The tuberculin test is the paradigm for this type of hypersensitivity.

Although the reactions obtained with the Schick and Dick tests are delayed in type, they are dependent on an entirely different mechanism from those due to tissue sensitivity. It should be clearly borne in mind that, unlike the other skin tests described in this review, the Schick and Dick reactions depend on the inherent toxic properties of the materials used for testing. Their injurious effects are exerted in persons who possess no specific neutralizing antitoxin. Hence, a positive Dick or Schick test indicates susceptibility in contrast to a positive reaction of the tuberculin type, which indicates previous infection with the pathogenic agent that may or may not have led to the emergence of resistance.

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The hypersensitivity established in a number of diseases may last for years or even a lifetime. Consequently the demonstration of dermal allergy to a given bacterial or viral agent, although it signifies a previous contact with a given infectious agent, does not necessarily mean that this agent is responsible for the disease immediately under consideration.

## SKIN TESTS EMPLOYING BACTERIA AND THEIR PRODUCTS AS ANTIGENS

### *Tuberculin Test*

It has been amply demonstrated that the most satisfactory method for tuberculin testing is the intradermal route (Mantoux).<sup>5</sup> The two tuberculin preparations now in use are O. T. (old tuberculin), introduced by Koch,<sup>2, 3</sup> and P. P. D. (purified protein derivative), isolated by Seibert.<sup>6, 7</sup> O. T. is a crude product that besides active skin-reacting principle also contains various other constituents of the tubercle bacillus. The only disadvantage of this product is the variation in the amount of skin-reacting substance in different preparations, depending on the culture medium used and the strain of tubercle bacillus employed. This objection has been overcome, however, by standardizing O. T. in tuberculous guinea pigs against a standard P. P. D. obtained from the National Institute of Health. The initial test dose of O. T. ordinarily used for intracutaneous testing contains 0.01 mg. of O. T. in a volume of 0.1 cc. (1:10,000).<sup>\*</sup> To avoid systemic reactions in persons suspected of having active tuberculosis, it is well to start with a dose of 0.001 mg. (1:100,000). If no reaction is produced with the initial dose, the concentration can be increased tenfold until 1.0 mg. has been injected. If this is negative, the succeeding dosage should be 5.0 mg. and 10 mg.† The usual procedure is to inject 0.01 mg. and to retest all negative reactors with 1.0 mg. With 1.0 mg. as the final dose a small proportion who fail to react may be called negative, although they might react to 10 mg. No case should be regarded as genuinely negative unless there has been a failure to react to 10 mg. of O. T.<sup>5, 8</sup>

A positive reaction is one that shows edema and redness of varying degree after forty-eight hours. Positive reactions should be arbitrarily classified +, ++, +++ or ++++, depending on the extent of the edema. A reaction showing some redness with definite edema more than 5 mm. in diameter but not exceeding 10 mm. is recorded as a + reaction. A ++ reaction is characterized by an area of redness and edema measuring from 10 to 20 mm. in diameter. A +++ reaction is characterized by marked redness and edema exceeding 20 mm. in diameter. A ++++ reaction consists of

marked redness and edema and an area of necrosis. If there is no edema at the site of injection, even if slight redness is present, the reaction should be recorded as negative.

Since dilute solutions of O. T. and P. P. D. deteriorate on standing, only freshly prepared solutions should be used. If dilutions are stored at refrigerator temperature when not in actual use, deterioration is less rapid, but such solutions should not be used after storage for longer than three or four days.<sup>9</sup>

It became obvious from Zinsser's<sup>10</sup> and Mueller's<sup>11</sup> work that the skin-reacting substance in tuberculin is associated with a protein or nucleoprotein fraction that can be separated from other serologically active compounds. Subsequently Seibert<sup>6, 7</sup> succeeded in isolating from O. T. a proteose or polypeptide (P. P. D.) that is responsible for the dermal reaction given by O. T. As supplied commercially at present, the first test dose consists of 0.00002 mg., and the second dose, for use when the reaction to the first is negative, of 0.005 mg. In terms of O. T. the first test dose of P. P. D. is equivalent to 0.01 mg. of O. T. and the second is somewhat stronger than 1 mg. of O. T.<sup>12</sup> The second-strength skin reaction must be read carefully, since Long and Seibert<sup>9</sup> and others<sup>13</sup> have stressed the fact that non-specific reactions are frequently seen with this strength. The positive reactions are graded as described for O. T.

In 1933, Grozin<sup>14</sup> made the observation that if a strip of adhesive plaster previously treated with tuberculin is applied to the unbroken skin, or if the skin is moistened with a drop of tuberculin and covered with adhesive, a susceptible person shows within twenty-four to forty-eight hours an inflammatory area of reaction limited to the surface covered by the adhesive plaster. He called this test the tuberculin patch test. Since then a number of variations have been used, the most usual one being filter paper impregnated with old tuberculin and held in close apposition to the skin with adhesive tape for forty-eight hours, at which time the tape is removed.<sup>15, 16</sup> Readings are made forty-eight hours after the removal of the tape. If the reaction is positive, an area of inflammation studded with tiny papules and vesicles appears, limited to the part in contact with the tuberculin. The ease of this technic aroused immediate interest. In 1939, Vollmer and Goldberger<sup>16</sup> showed a 100 per cent conformity between the tuberculin patch test and the Mantoux test using first strength P. P. D. or 0.01 to 1.0 mg. of O. T. In Smith, Faulkner and Cordi's<sup>17</sup> study only 6 of 223 negative reactors to the patch test turned out to be positive by the Mantoux test after a comparatively strong dose of O. T. These authors conclude that their cases responded to the patch test in nearly the same degree as to 0.1 mg. of O. T. Hence, it appears that the patch test is a suitable screening test and would be highly efficient if followed when negative by an intradermal inoculation

\*In preparing dilutions of O. T., each cubic centimeter of undiluted O. T. is assumed to contain 1000 mg. of tuberculin. Thus, a 1:10,000 dilution of O. T. contains 0.01 mg. of O. T. in 0.1 cc.

†With these higher doses a control injection of the medium alone should be used to rule out nonspecific reactions.

with 1.0 to 10.0 mg. of O. T. or second strength P. P. D.

It has been amply demonstrated that a positive tuberculin skin test means past or present infection with the tubercle bacillus.<sup>5</sup> The question arises concerning the frequency with which a negative test may occur in persons who have previously been infected. Lloyd and MacPherson<sup>18</sup> reported that of 303 healthy London children who reacted to 1.0 mg. of O.T., 2 per cent became negative to that dose two years later. Nelson, Mitchell and Brown<sup>19</sup> were able to find calcification by chest films in 43 per cent of 27 persons who were negative to the P. P. D. dose equivalent to 1.0 mg. of O. T. Dahlstrom<sup>20</sup> reported that 11.1 per cent of 2490 persons who were tuberculin positive to 1.0 mg. of O. T. or the equivalent P. P. D. became negative within five to fifteen years. Seventy per cent of those who became negative were originally weak reactors. Thus, it has been recently demonstrated that tuberculin sensitivity may be lost unless stimulated periodically by reinfection with the tubercle bacillus. Perhaps this fact is not yet clearly recognized by many clinicians.

The state of present knowledge does not permit a definite statement whether a positive tuberculin test is an asset or a liability. There have been a number of publications<sup>21-25</sup> that indicate that a positive test is a definite index of relative immunity. On the other hand, there have been reports in which the incidence of the development of tuberculosis has been higher in tuberculin-positive groups than in tuberculin-negative groups.<sup>26-28</sup> Still other publications have failed to indicate that there is any difference in the incidence of pulmonary tuberculosis between negative and positive reactors.<sup>29-31</sup> At the Harvard Medical School in the last fifteen years the number of cases of tuberculosis have been almost evenly divided between positive and negative reactors.<sup>32</sup>

The clinician is most interested in whether the symptoms presenting in a given case are the result of an acid-fast infection. In most cases it is only the negative result that is of diagnostic aid, since, except in the terminal stages of the disease, a genuinely and persistently negative reaction to 10 mg. of O. T., with rare exception, rules out progressive infection.<sup>5, 8, 33</sup> Although dehydration, intercurrent infection, early stages of pleural and peritoneal effusion and the terminal stages of tuberculous infection are not infrequently accompanied by a temporary absence or depression of reactivity, sensitivity is not depressed to such a degree during uncomplicated tuberculosis that 10.0 mg. of O. T. fails to provoke a reaction.

### *Brucella Skin Test*

The development of dermal sensitivity following brucellosis was first investigated in 1918 by Fleischer and Meyer.<sup>34</sup> Sufficient data have since been accu-

mulated to show that dermal sensitivity to *Brucella* antigens occurs regularly enough following brucellosis so that its demonstration can be used as a diagnostic procedure.<sup>35-39</sup> It is apparently much more sensitive and is present in a much higher percentage of infected persons than are serum agglutinins. Huddleson<sup>40</sup> has shown that if the agglutination test alone had been used as a diagnostic procedure, it would have failed to detect 86.9 per cent of 845 cases of brucellosis that gave positive dermal reactions.

Two antigens are at present in wide use to elicit skin reactivity: a heat-killed suspension of *Brucella* organisms in saline solution, and brucellergen, a so-called "nucleoprotein" from *Brucella* organisms, developed by Huddleson and his colleagues.<sup>40</sup> Both these antigens appear to be effective in eliciting dermal sensitivity. The whole organism, however, is likelier to produce local sloughs and systemic reactions.<sup>41, 42</sup> Since there is no evidence that the whole organism gives better results, brucellergen appears to be the antigen of choice.

The bulk of evidence indicates that a positive skin test means past contact with any one of the *Brucella* organisms. Gould and Huddleson<sup>43</sup> regard the intradermal test with brucellergen as an extremely reliable indicator of *Brucella* infection. They believe that if the test is negative, brucellosis can usually be ruled out. In only 1 out of 925 cases negative to the intradermal test were the agglutination and opsonic tests indicative of past infection. On the other hand, it has been shown by others that some persons proved by the isolation of the organisms to have brucellosis have had negative skin reactions.<sup>35, 44, 45</sup> The incidence of a negative reaction in the presence of chronic disease has been reported as varying from 5.5<sup>46</sup> to 39 per cent.<sup>47</sup> Thus, whereas a positive test denotes previous contact with *Brucella* organisms, a negative test does not necessarily rule out previous infection.

Since the skin hypersensitivity lasts for many years, a positive test does not necessarily mean present active disease but may indicate a past contact with the organisms. The status of a patient with a positive skin test can be established only by determining the phagocytic activity of the leukocytes in the presence of *Brucella* organisms.<sup>40</sup>

The skin test must not be performed before blood has been drawn for the agglutination or opsonocytophagic determinations, because the introduction of the antigen may stimulate the production of opsonins and agglutinins. This stimulation has been observed with both brucellergen<sup>48</sup> and whole organisms.<sup>49, 50</sup>

The brucellergen test is performed by injecting 0.1 cc. of a standardized solution intradermally on the volar surface of the forearm. The test is read at forty-eight hours, and the reaction is considered positive if, in addition to an area of redness, there is also edema or induration that measures at least

5 mm. in diameter. If whole organisms are used, the reaction should be observed on the fourth and seventh days.

#### *Chancroid Skin Test (Ito-Reenstierna Test)*

In 1913, Ito,<sup>51</sup> using a vaccine prepared from a culture of *Haemophilus ducreyi*, was able to demonstrate the development of dermal allergy in chancroidal infection. The diagnostic value of this test was confirmed by Reenstierna,<sup>52</sup> and it has come to be known as the Ito-Reenstierna test. For years a skin-test vaccine (Dmelcos vaccine) has been prepared commercially in France and used extensively in Europe and Canada; this preparation has never been available in this country owing to public-health regulations. Because of this and the difficulty American workers experienced in growing the etiologic agent, pioneer work in this country on the value of the intradermal test was done in 1935 by Cole and Levin<sup>53</sup> with pus obtained from unbroken buboes. These authors stressed the need for further investigation on the growth requirements of *H. ducreyi*. Within two years methods for growing the organism were published.<sup>54, 55</sup> Vaccines prepared from these cultured organisms have subsequently been shown to be highly satisfactory for use as antigens in eliciting dermal hypersensitivity<sup>56-58</sup> and are now commercially available.

It is generally accepted that the Ito-Reenstierna test is of definite aid in the differential diagnosis of the venereal bubo since the buboes of syphilis, gonorrhea, chancroid and lymphogranuloma inguinale and the pseudobubo of granuloma inguinale frequently simulate one another. In the experience of most investigators the test is highly reliable. Kornblith and his co-workers<sup>59</sup> have found the test to be positive in 95 per cent of 93 proved cases of chancroid. Cole and Levin<sup>53</sup> have demonstrated negative tests in lymphogranuloma inguinale, primary and secondary syphilis, gonorrhea and granuloma inguinale, the diseases likeliest to be confused with chancroid clinically.

There is some disagreement in the literature concerning when the skin test becomes positive following infection. Reports have varied from six to ten days<sup>60</sup> to five weeks.<sup>61</sup> Greenblatt and Sanderson<sup>58</sup> have obtained positive reactions regularly from the twentieth day onward in experimentally induced infections. A positive test is uniformly obtained by the time the buboes appear.<sup>62</sup>

Since dermal allergy may last for years, possibly a lifetime, a positive reaction commits one to the diagnosis of chancroid only when the Frei test, Wassermann test and dark-field examination as well as biopsies and smears for granuloma inguinale, are negative. It is difficult to reconcile the favorable reports in the literature with the statement in Circular Letter No. 74 from the Office of the Surgeon General<sup>63</sup> that the intradermal test is not recommended for the diagnosis of chancroid.

The test is performed by injecting 0.1 cc. of the vaccine intradermally into the volar surface of the forearm. The reaction is positive if an area of induration measuring at least 8 mm. and an area of erythema 14 mm. in diameter are present forty-eight hours after injection. Nonspecific reactions may appear in twenty-four hours, but they usually disappear within forty-eight hours. The local reaction may last for weeks.

#### *Whooping Cough Skin Test*

The use of the skin test to determine immunity or susceptibility to whooping cough must be considered as still in the experimental stage. A skin test should not be considered satisfactory unless the results correlate with the incidence of clinical and bacteriologically proved cases after subsequent exposure. As yet this has not been done in the case of the whooping cough skin test.

*Haemophilus pertussis* contains at least two antigens — a so-called "agglutinin" and a thermolabile toxin — that are capable of eliciting dermal reactions. In the past the skin test as a method for determining susceptibility was unsatisfactory because the preparations used contained both these antigens. By means of supersonic vibration, Flosdorf and his associates<sup>64</sup> have been able to separate the agglutinin from the toxic components. This material has been used in an endeavor to establish immunity or susceptibility by means of the response obtained on intradermal inoculation.<sup>65-67</sup> The antigen is injected intradermally, and readings are made in half an hour and twenty-four hours. In immune persons two types of response have been obtained — an immediate wheal-like reaction and a delayed or tuberculin type of reaction. Some immune persons show both these reactions, whereas others show only one of them. Felton and Flosdorf<sup>66</sup> have shown that there is a close correlation between the agglutination titer of the blood serum (which is thought to be an index of immunity<sup>64, 68</sup>) and the positive skin test. In only one case did they find the agglutinating titer high and the skin test negative.

Flosdorf, Felton, Bondi and McGuiness<sup>67</sup> have recently summarized their experience using the agglutinin as an antigen in performing the whooping cough skin test. Of 122 babies from six to fourteen months of age with no history of whooping cough, only 1 gave a false-positive test. Eleven per cent of those with a positive history and 8 per cent of the vaccinated group, however, were negative. It is possible that some of the children with positive histories were infected with *Bacillus parapertussis* and hence a positive skin reaction did not result.<sup>64</sup> Although the results obtained with the detoxified antigen are encouraging, more work will obviously have to be done before it can be accepted that a positive test means immunity.

As outlined above, there are two types of dermal allergy. One depends on the presence of circulating antibodies, whereas the other is a true tissue sensitivity. In the former type a response is obtained fifteen minutes after inoculation of the antigen and usually disappears in three hours, whereas in the latter the reaction is always of the delayed type. Since both types of reaction may be elicited in the whooping cough skin test, it seems probable that the material used may contain two antigens — one reacting with the circulating antibody and the other acting directly on the tissue cells.

In 1940, Strean et al.<sup>69</sup> described a skin test with purified pertussis toxin, which he believed might be used to indicate susceptibility or immunity. An immune response is obtained only in those who have recovered from the disease or those immunized with the toxoid. It is interesting that a susceptible reaction is found in those who have been vaccinated with whole Phase I organisms. Silverthorne, Fraser and Brown<sup>70</sup> have recently repeated Strean's work, however, and have shown that the toxin does not distinguish between those who have had the disease and those who are presumably susceptible.

#### *Tularemia Skin Test*

The early work on the diagnostic skin test in tularemia was done using whole organisms killed with formaldehyde.<sup>71</sup> The sensitivity that develops following tularemia is apparently of a very high degree, and a few patients have suffered alarming constitutional reactions following the use of this skin-test material.<sup>71</sup> Because of these reactions, Foshay<sup>72</sup> prepared a detoxified antigen by treating the organisms with nitrous acid. This antigen is apparently bland and does not produce constitutional reactions. The skin test with this material appears to be highly specific and is not positive in patients with brucellosis whose serums are able to agglutinate *Pasteurella tularensis*. The reaction becomes positive within the first week of the disease and is probably lifelong in duration. Since the agglutination test does not become positive until the second week of the disease, a positive skin test is of great value in the early diagnosis of tularemia. Friedewald and Hunt<sup>73</sup> have skin-tested 32 proved cases of tularemia with Foshay's antigen and found the dermal reaction positive in all. They have clearly shown that the test becomes positive within the first week of the disease. These same authors skin tested a large number of patients with numerous clinical conditions and found no false-positive reactions.

The skin test is performed by injecting 0.05 cc. of the antigen intracutaneously on the volar surface of the forearm. A positive test is a delayed tuberculin-like reaction consisting of erythema and induration. Nonspecific reactions appear early and usually fade rapidly after forty-eight hours, whereas a specific reaction generally persists for a week or

longer. Unlike the antigens used in the Brucella skin test, the antigen used in the diagnosis of tularemia does not stimulate to any marked degree the production of agglutinins.

To make a diagnosis of tularemia before the development of dermal hypersensitivity, Foshay has described a test<sup>74, 75</sup> in which antitularense goat or horse serum is injected intradermally to detect circulating bacterial antigen such as might be present early in the disease. In all the dermal tests previously described in this paper, antigen is injected to detect circulating or fixed antibody. In this test antibody is injected to demonstrate antigen. Presumably this type of test should be positive early in the infection. Four one hundredths cubic centimeter of a 1:10 dilution of serum is injected intradermally, accompanied by the same volume of diluted normal serum as a control. In most cases positive reactions appear almost immediately and consist of a wheal and areola of erythema. This test has been reported as being positive as early as eight hours after the initial chill. Friedewald and Hunt<sup>73</sup> believe that if the antiserum test shows a definitely positive reaction and the control serum is negative, a diagnosis of tularemia can be made with reasonable certainty. In their experience, however, the controls were positive in a high percentage of cases, so that they were able to diagnose only a third of the cases by this method. The same authors<sup>73</sup> used convalescent serums from cases of tularemia and found that the reactions obtained in normal patients and those with tularemia were variable and unreliable. The usefulness of this test is obviously limited because of the positive skin reactions obtained with the control serum.

#### *Francis Test*

In 1929, Tillet and Francis<sup>76</sup> showed that specific capsular pneumococcal polysaccharides when injected intradermally into patients convalescent from pneumonia caused an immediate wheal and erythema that appeared in ten to twenty minutes and faded in one to two hours. The polysaccharide causing the reaction was found to be always homologous in type with the pneumococcus causing the pneumonia. The patient's capacity to react became manifest coincident with or shortly before recovery from the infection and was invariably associated with the presence of type-specific antibodies in the blood. In 1930, Francis and Tillet<sup>77</sup> extended their observation and reported that recovery from Type 1 pneumonia was associated with the development of a positive skin reaction to Type 1 polysaccharide. In every case in which the skin test became positive the patient recovered. In Finland and Sutliff's<sup>78</sup> experience, however, only half the Type 1 and two thirds of the Type 2 and 3 patients who recovered gave a positive reaction. In 1933, Francis<sup>79</sup> recommended a skin test with specific capsular poly-

saccharide of the pneumococcus as a guide to serum therapy. He believed that the skin test was a valuable aid to serum therapy and of definite prognostic aid. When the test was negative, he believed that further serum therapy was indicated. The value of this test as a guide to serum therapy has been repeatedly confirmed.<sup>80-82</sup>

The development of a positive Francis reaction is due to the local union of polysaccharide and its specific antibody in the skin. A relatively large amount of circulating antibody must be present to produce the dermal reaction.<sup>82</sup> During the course of severe pneumonia the skin may lose its ability to react owing to the general toxemia, and this probably explains the negative reactions observed in patients who die of pneumonia despite the presence of appreciable amounts of circulating antibodies. In Wood's<sup>82</sup> series of serum-treated cases, in every case in which a crisis occurred the Francis skin reaction became positive several hours before or during the fall of temperature. No patient who failed to develop a positive skin reaction survived the pneumonia. Wood believed that the test could also be employed as an aid in the early diagnosis of the complications of pneumonia. In every case in which fever persisted in the presence of a positive skin reaction, pleurisy with effusion, empyema, meningitis or endocarditis was subsequently demonstrated.

As in any skin test, there are false-positive reactions to the Francis test. MacLeod, Hoagland and Beeson<sup>81</sup> have found 13 per cent false positives and Wood<sup>82</sup> 9 per cent. Obviously, because of these false-positive reactions the Francis test cannot be used as an index of immunity unless the reaction is negative when it is first employed. When it is observed to change from negative to positive, recovery seems assured unless complications are present. A persistently negative reaction means a less favorable prognosis. It goes without saying that the etiologic organism must be typed so that the homologous polysaccharide can be employed.

#### *Skin Tests for Influenza-Bacillus Infections*

In 1939, Dingle and Fothergill<sup>83</sup> isolated a specific carbohydrate from the Type B influenza bacillus. Using this material as in the Francis test, Dingle and Seidman<sup>84</sup> were able to obtain a reversal of the test from negative to positive in 5 cases of influenza-bacillus meningitis treated with rabbit antiserum. The test failed to be reversed in cases treated with horse antiserum. This may be related to the fact that precipitins are less readily produced in horse serum than in rabbit serum. There were no false-positive reactors among the controls. Although this test is based on firm bacteriologic principles, much more work will have to be done before it can be recommended.

(To be concluded)

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31251

#### PRESENTATION OF CASE

A fifty-six-year-old Greek woman was admitted to the hospital complaining of chills and fever and a mass in the left upper quadrant.

Three years before admission the patient entered another hospital because of a painful mass in the left upper quadrant and easy bruising of six months' duration. She had tired easily and had lost about 20 pounds in weight during the preceding year. She also complained of episodes of red urine and a bloody vaginal discharge. Physical examination at that time revealed a small wizened woman who showed evidence of considerable weight loss. There were petechiae on the palate, and a tourniquet test was positive. Several quite large purpuric areas were seen on the extremities, especially on the legs. The liver was felt by one observer two to three fingerbreadths below the right costal margin. The spleen extended to 10 cm. below the left costal margin. Hinton and Wassermann tests were negative. The urine was normal. The red-cell count was 3,500,000, with 10.5 gm. of hemoglobin and a hematocrit of 30 per cent; the white-cell count was 2100, with 55 per cent neutrophils, of which 10 per cent were band forms, and 42 per cent lymphocytes. The red cells showed mild anisocytosis, and the platelets were markedly reduced, numbering 59,000 per cubic millimeter. A gastric analysis showed no free acid in the fasting specimen and 17 units of total acid after histamine. The icteric index was normal. X-ray examination of the long bones was negative. During the twenty-three hospital days her temperature was 98.6°F., except for a rhythmic rise to about 100°F. every third day. She was given four x-ray treatments of 65 r each over the splenic area, with no change in the size of the spleen. Five days after x-ray treatment she was discharged unimproved.

The patient had taken quinine irregularly once or twice a week for about a year, with some relief. During the five months before admission to this hospital she experienced regular attacks of chills and fever, occurring every seventy-two hours between 6:00 and 7:00 p.m. A backache in the upper

lumbar region was present at all times of the day and had persisted since the onset of the present illness. For approximately two months before admission her appetite had been poor, and she had some exertional dyspnea and orthopnea and a slight cough.

The patient was born in Greece and had lived there for eighteen years. She came to the United States thirty-eight years previously and had worked in a cotton mill in Massachusetts. She was married at the age of twenty-six and had had two full-term babies, both delivered by cesarean section. One infant was stillborn, and the other died at fourteen days. Until the present illness she had been in good health. She remembered no infections or other diseases.

Physical examination revealed an emaciated, chronically ill-appearing woman in no distress but for occasional stabs of pain in the left upper quadrant and epigastrium, which were induced by moving about. The skin was warm and dry and had a slight yellow tinge. The peripheral lymph nodes were not remarkable. There were many varicose veins over the legs and thighs, and fairly prominent superficial veins over the lower chest and abdomen. There were no ecchymoses. There was slight pitting edema of the legs. The left pupil measured 2 mm. in diameter and was fixed and slightly irregular. The neck veins pulsated in the erect and supine positions. The lung fields were clear and hyperresonant. The left heart border was at the mid-clavicular line. A Grade 2 blowing systolic murmur was heard over the entire precordium and was loudest at the left sternal border in the fourth interspace. The spleen was firm, smooth and mobile; it extended into the left lower quadrant and a small distance across the midline at the level of the umbilicus. The liver edge was sharp and extended three fingerbreadths below the costal margin. There was no ascites. Vaginal and rectal examinations were negative. The tendon reflexes of the lower extremities were absent.

The temperature was 99.6°F., the pulse 90, and the respirations 20. The blood pressure was 140 systolic, 70 diastolic.

On admission the blood contained 3,200,000 red cells, with 7 gm. of hemoglobin and a hematocrit of 26 per cent. The white-cell count was 2400, with 61 per cent neutrophils and 35 per cent lymphocytes. A reticulocyte count was 1.2 per cent. The platelets were slightly reduced in number. The bleeding time, clotting time and clot retraction were normal. The urine was straw-colored, with a specific gravity of 1.018, and gave a +++ test for albumin; the sediment contained an occasional red cell and hyaline cast. A catheterized specimen showed no growth on culture. A stool was dark, formed and guaiac negative. The sedimentation rate and a van den Bergh test were normal. The serum nonprotein nitrogen was 36 mg. per 100 cc., and the protein

\*On leave of absence.



5.58 gm., the albumin-globulin ratio being 1.71. The phosphorus was 4.5 mg. per 100 cc., and the alkaline phosphatase 2.9 Bodansky units. A Hinton test and a spinal fluid Wassermann test were negative. A cephalin flocculation test was +++ in forty-eight hours, and the prothrombin time was 21 seconds (normal, 18 to 20 seconds). A bromsulfalein test showed 30 per cent retention forty-five minutes after the injection of 5 mg. per kilogram. An electrocardiogram was normal. A phenolsulfonphthalein test showed 55 per cent excretion in two hours, and the urine concentrated readily to a specific gravity of 1.020. A lumbar puncture yielded normal findings.

X-ray examinations of the chest and abdomen showed the left diaphragm to be elevated, with the heart in a transverse position. The aorta was tortuous, with some calcification in the arch. A large mass extended down from the left upper quadrant to overlie the sacrum and the left iliac wing, displacing the colon downward and the stomach to the right. The left kidney outline was seen through the mass. A gastrointestinal series was negative. No esophageal varices were seen.

At 5:30 p.m. on the second hospital day the patient had a severe chill. At 7:00 p.m., the temperature rapidly rose to a peak of 106°F., and during the following six hours gradually returned to normal. The pulse and respiratory curves closely followed the temperature curve. Four similar episodes of chills and fever occurred during the following two weeks at regular seventy-two-hour intervals. Blood cultures taken during the chills and during the peak of the fever showed no growth, and blood smears taken at the same times showed no parasites. Because the spleen was firm and presumably fibrotic, a splenic puncture was deemed safe and was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. WILLIAM DAMESHEK\*: Chills, fever and a mass in the left upper quadrant in a Greek woman might conceivably mean malaria. So we immediately have a rather plausible diagnosis to start with. Of course there are other possibilities that I shall introduce as I go along.

There were petechiae on the palate, and a tourniquet test was positive. These findings usually indicate a platelet deficiency and remind me of what I like to call "the dental plate test." If you have a patient with thrombopenia, due to whatever cause, and if he happens to have dental plates, when the upper plate is taken out, you will find petechiae on the palate, due to the suction of the dental plate. It is a fairly good test. The chances are that this woman had a low platelet count.

The liver was felt two or three fingerbreadths below the right costal margin, and the spleen ex-

tended a handbreadth below the left costal margin. That signifies a rather sizable organ. So she had hepatosplenomegaly and purpura, probably thrombopenic in type.

The Hinton and Wassermann tests were negative. Apparently we do not have to be concerned about syphilis.

There were 3,500,000 red cells, with 10.5 gm. of hemoglobin. In other words, she had a reduction in hemoglobin slightly out of proportion to the reduction in red-cell count. To digress from the case for a moment, let me say a word about the color index. This is calculated readily by taking the percentage of hemoglobin and dividing by the first two figures of the red-cell count. If the hemoglobin is 50 per cent, and the red count 5,000,000, the index is 0.5. If one is dealing with grams of hemoglobin, as we now are, we multiply the figure for grams by 3 and divide by the first two figures of the red count. At the time of admission to the other hospital, it was  $10.5 \times 3 \div 35$ , or 0.9, which indicates some degree of hypochromia, or hypochromic anemia.

Whenever I see a Greek or Italian woman with hypochromic anemia I wonder about Mediterranean anemia of the target-oval-cell type, a mild form of Cooley's anemia. The mean corpuscular volume was  $30 \times 10 \div 3.5$ , or 86, which is either less than normal or approximately normal. There was a definite leukopenia, the white-cell count being only 2100, with 55 per cent polymorphonuclears. Although the lymphocytic proportion was increased, it was really only relatively increased. Thus, although they numbered 42 per cent of 2100, this is only 20 per cent of 4000 white cells. So she really had no absolute increase, in fact the lymphocytes were somewhat diminished. The granulocytes were 55 per cent of 2000, which is a definite granulocytopenia. The normal granulocyte proportion is 70 per cent of 7000 to 8000, and here it was 55 per cent of 2000, or only 1200 to 1300 in absolute numbers. So she had leukopenia, granulopenia and anemia. The platelets were reduced, numbering 59,000. She had then what I like to call "pancytopenia," a reduction in all the cellular elements in the blood, including the red cells, white cells, granulocytes and platelets.

Pancytopenia may be due to various conditions involving the marrow: aplasia, hyperplasia, leukemia and sarcomatous infiltration. Pancytopenia is also frequently associated with splenomegaly, the bone-marrow being either normal or hypercellular. There may be total pancytopenia, or anemia, leukopenia or thrombopenia may dominate the clinical picture. In this patient, the thrombocytopenia was most evident and the patient had extensive mucous membrane bleeding.

X-ray studies of the bones were negative which helps to exclude Mediterranean anemia, myeloid sclerosis, Gaucher's disease and sarcoma.

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"During the twenty-three hospital days the temperature was 98.6°F., except for a rhythmic rise to about 100°F. every third day." This I think is the leading theme in this case. It is repeated throughout the history. This one-two-three rhythm may be said to represent the ominous rumbling in a developing "symphonic" situation, which we shall find out more about as we read the history.

The fact that the spleen did not change in size after x-ray treatment helps to exclude lymphosarcoma of the spleen, Hodgkin's disease, leukemia and related conditions.

We come next to the second phase of this woman's illness. She had taken quinine irregularly once or twice a week for about a year after she left the hospital "with some relief." That statement may or may not be of diagnostic value.

The exertional dyspnea, orthopnea and cough might indicate a pulmonary infection or the beginning of heart failure at the age of fifty-six, with anemia and chronic illness.

We find that the patient was born in Greece and lived there for eighteen years. We are not sure whether she had an infectious disease when she was in Greece, and we do not know whether she came from the northern or southern part.

DR. BENJAMIN CASTLEMAN: Dr. Cotzias, can you enlighten us about that?

DR. GEORGE C. COTZIAS: She came from southern Greece.

DR. DAMESHEK: That may mean something, since malaria is more frequent in the southern section.

Anyone is apt to have pain with a large spleen from whatever cause, either infectious or otherwise. It is apt to become infarcted from time to time, and a perisplenitis often develops. Pain on motion is frequently present in these cases.

The varicose veins and the prominent veins over the chest and abdomen suggest a delay in portal circulation with some collateral circulation.

What significance the systolic murmur has, I cannot say. She might have had it before or she might have developed it recently. It might have had something to do with the anemia or arteriosclerosis, or both.

I suppose that albuminuria in a woman of fifty-six who has been ill and has some degree of arteriosclerosis of the kidneys is of no significance.

A catheter specimen of urine was cultured and yielded no growth. That is an important test for urinary infection and helps to rule out colon-bacillus infection.

The patient on entry to this hospital had a red-cell count of 3,200,000, with 7 gm. of hemoglobin. So multiplying the grams of hemoglobin by 3 and dividing by the first two figures of the red count, we get the figure 0.65, or a hypochromic, low color-index anemia, and  $26 \times 10 \div 3.2$  gives a mean corpuscular volume that is diminished, a hypochromic, microcytic anemia. She had leukopenia, granulo-

cytopenia of an absolute variety, with no abnormal cells. There is no statement about monocytes. Since monocytes are frequently miscalled lymphocytes, perhaps there were monocytes included in the lymphocytic count. A monocytosis might be expected in malaria. The reticulocyte count was normal. She had lost the marked thrombocytopenia and the abnormal clot retraction that she had on admission to the hospital three years previously.

I suppose that the van den Bergh was a quantitative test for bilirubin and was within normal limits, indicating that she did not have jaundice, which helps to exclude the question of hemolytic disease. One always has to consider this possibility with an enlarged spleen, but if the bilirubin is normal one can almost always exclude it. The albumin-globulin ratio was essentially normal, showing no hyperglobulinemia and no reversal of the albumin-globulin ratio. This tends to rule out such conditions as multiple myeloma and Boeck's sarcoid. The bromsulfalein excretion was definitely delayed, indicating some degree of hepatic insufficiency.

"No esophageal varices were seen." That is a finding that helps to rule out cirrhosis, at least of a marked degree.

"Because the spleen was firm and presumably fibrotic a splenic puncture was performed." That apparently is the end of the story. We do not know whether the patient recovered after this procedure or whether she died.

In summary, this was a woman who came from Greece to this country a long time ago and had apparently been well since. Three years previously she went to a hospital, essentially for a hemorrhagic condition. At that time she showed an outstanding thrombocytopenia with the clinical evidence of purpura, so that we have to say that she had thrombocytopenic purpura. This condition may be idiopathic, or it may be due to many causes, such as leukemic or aplastic bone marrow or various types of splenic disease, which I like to call "hypersplenism." This may result in either leukopenia, thrombopenia or anemia, or in all three together. In some cases of hypersplenism, there is a marked degree of thrombocytopenic purpura. I therefore explain the first episode three years previously on the basis of an enlarged hyperactive spleen. We do not know the cause of the enlarged spleen at that time. It may have been due to infection, but she left the hospital and took quinine for a while, with perhaps some response.

Five months before admission to this hospital she had regularly recurring chills and fever every seventy-two hours. We also know that she had had it to some degree three years previously. The only disease that I know of that causes recurring fever and chills every seventy-two hours at exactly the same time of day for a period of many months is malaria of the quartan type. It is true that other conditions associated with splenomegaly cause

fever. One of the most frequent types that we have to contend with is that due to lymphoma, Hodgkin's disease and atypical leukemia. If this patient had had an irregular fever coming at various times or had had a relapsing fever of the Pel-Ebstein variety, we should have concluded that she had one of these conditions. Some cases of brucellosis, or undulant fever, have the same type of fever chart. But this woman did not have an irregular type of fever or relapsing fever. She had a regular one coming on at the same time of evening, between 6:00 and 7:00 p.m.

Infections other than malaria have to be considered, such as tuberculosis and subacute bacterial endocarditis. The heart murmur was systolic in type but the blood cultures were negative, and furthermore, subacute bacterial endocarditis does not give this type of fever. It is true that we have to consider atypical leukemia and myeloid metaplasia, but she had no myelocytes and no nucleated red cells. The outstanding feature of this case is certainly this rhythmic fever; in a Greek woman with a big spleen I do not believe that it can be anything but malaria.

Quartan malaria is the slowest of the malarial infections and is the one that takes longest to incubate. It may be present for a number of years and then vanish. It may isolate itself in the reticulo-endothelial system, notably the spleen. Splenic enlargement may occur, and the parasites may never be demonstrated in the blood. I do not know how the tests were done; probably with extreme care. I do not know whether they made thick smears or whether a sternal puncture was done. Dr. Castleman let me look at a blood smear, but it was entirely normal. It was not a thick preparation. If one has a case of suspected malaria in which the blood smears appear normal one of several things can be done. A sternal puncture, which is simpler than a splenic puncture, and without danger, or an adrenalin injection may be done. The latter is a favorite maneuver in the Latin-American countries and in France. Or one can do a splenic puncture. Whether the splenic puncture in this case showed malaria, I do not know. To my mind the present case was dominated by rhythmic fever, which makes malaria likely.

DR. CASTLEMAN: Dr. Richardson, have you any suggestions?

DR. WYMAN RICHARDSON: I never saw this patient, but I feel the same way about it that Dr. Dameshek does.

#### CLINICAL DIAGNOSIS

Quartan malaria.

#### DR. DAMESHEK'S DIAGNOSIS

Quartan malaria.

#### ANATOMICAL DIAGNOSIS

Quartan malaria.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The intern and resident staff and the visiting men all looked at the smears, thick and thin, and were unable to find any malarial parasites. The material that I received from the spleen was composed almost entirely of histiocytes. I looked carefully for parasites and was unable to find any. There were no hemosiderin granules, which one usually finds in a malarial spleen. Dr. Volweiler took the slides to the Department of Tropical Medicine at the Harvard Medical School, and Dr. Geiman kindly examined them. We shall hear from him now.

DR. Q. M. GEIMAN: Dr. Volweiler brought films of the splenic puncture to me for examination and told me the history of the case. The history immediately interested me greatly because of the number of cases of so-called "transfusion malaria" that have occurred at various hospitals in Boston. Blood films from the patients are brought to us for examination from time to time. Although we find positive films in these patients, the donors of the blood seldom give a history of recent clinical malaria and no malaria parasites are found.

Since this patient was born in Greece and was having periodic chills and fever every seventy-two hours, quartan malaria seemed to be the first possibility, at least in my experience; the patient could have obtained the infection a number of years previously. The films from the splenic puncture were examined, and parasites were not found at that time. I might say that the films were examined for ten minutes, which is in excess of the usual five minutes for the study of such films.

I asked Dr. Volweiler to make films, both thin and thick, at intervals during a period of several days with the hope that we might catch some of the parasites during their asexual cycle in the peripheral blood. These films were brought to me, and the thick film taken at 4:00 p.m. on February 6 yielded one parasite, which was an unmistakable half-grown schizont, with typical cytoplasm, chromatin and pigment. With that one parasite, I went back through the splenic film, examining it from one end to the other, and fortunately another parasite, a segmenter, was found that determined the exact species, *Plasmodium malariae*. The examination of additional blood films, made at intervals, produced a total of ten unmistakable and two doubtful parasites. That result of prolonged microscopical study gives you an idea of the scarcity of malaria parasites in this patient. It is outstanding that such a low concentration of parasites could be responsible for clinical malaria.

I thought that you might be interested in a case reported by Shute,\* which emphasizes the same point. The case seen by Shute and this case demonstrate that the parasite of quartan malaria can persist in a patient for long periods of time and eventually give rise to a relapse of malaria. At the Children's Hospital, Boston, one of the donors of blood for a case of transfusion malaria had been in this country thirty-seven years without ever having clinical malaria. What the basis for this latency is we do not know, but new information is being accumulated which suggests that there are tissue stages of the parasite in the spleen or other reticulo-endothelial tissue that are the reservoir of organisms for this small dribble of parasites into the circulating blood and the origin of parasites that cause relapsing malaria.

DR. CASTLEMAN: I might add that the patient has received Atabrin and is now free from chills and fever.

## CASE 31252

### PRESENTATION OF CASE

A fifty-eight-year-old man was admitted to the hospital because of chills, fever and vomiting.

Twenty-two months before admission a pilonidal sinus, which during the previous twenty-five years had frequently opened and discharged pus, again began to drain. A few days later he noticed, while at work, that the right leg was becoming heavy and lifeless. By the end of the day the entire right leg was paralyzed without obvious sensory disturbance. He was admitted to a community hospital. Motor function and strength slowly returned, but the patient was unable to stand and he remained incontinent of urine and feces. He was then transferred to this hospital, where he remained for an additional seven weeks, during which time he learned to walk slowly with a cane and his bladder function improved so that he could retain his urine for about an hour. Infarction of the lower spinal cord was thought to be the likeliest diagnosis. During the entire hospital period, after the first four days, the temperature, pulse and respirations were normal. The urine gave a +++ test for albumin constantly, the specific gravity was 1.010 to 1.018 and the sediment almost always contained innumerable white cells. The red-cell count was 3,000,000, and the white-cell count 6000 to 8000. A month after discharge he began to notice slight swelling of the ankles in the evening, but examination of the heart was negative and he had no dyspnea, orthopnea, precordial pain or palpitation. His walking slowly improved, but he continued to have incontinence. Eighteen months after discharge he developed an ulcer on the sole of the left heel, which slowly be-

came larger and drained seropurulent fluid. About a month later, or approximately one month before this admission, he began to notice malaise and progressive weakness. The legs swelled more than usual, and the ulcer of the left heel became worse. On the day before admission he had several shaking chills, fever and drenching sweats. He vomited and for a brief period became quite dyspneic.

He had had pneumonia and empyema eighteen years before entry.

Physical examination revealed an obese, pale, febrile, perspiring man. He moved himself about in bed with little help from his legs, which were quite weak. He was surrounded by a strong uriferous odor. A deep penetrating ulcer on the left heel drained thin serous fluid. The tongue was coated and fiery red but not smooth. The neck was not stiff. Examination of the chest suggested emphysema, and moist crackling rales were heard in the right axillary line. The heart was enlarged to 10 cm. to the left of the midsternal line. The sounds were distant. There was an occasional, irregular beat. A soft, rumbling, apical murmur lasted throughout systole and early diastole. The aortic and pulmonic second sounds were equal. The liver extended 2 cm. below the right costal margin. There was no costovertebral-angle tenderness. There was minimal pitting edema of the left leg. Examination of the rectum revealed a loose anal sphincter. The terminal portion of the penis was macerated, swollen and chronically infected. The right leg was weaker than the left, and the tendon reflexes of the right knee and ankle were stronger than those on the left. There was a right Babinski. There was decreased pain and temperature response over the left leg, and diminished vibration sense of the right leg. These changes were seen on the trunk and shaded off to normal about two segments below the nipples. The remainder of the neurologic examination was negative.

The temperature was 99.0°F., the pulse 90, and the respirations 20. The blood pressure was 93 systolic, 50 diastolic.

The urine was cloudy, acid in reaction, with a specific gravity of 1.014, and gave a ++ test for albumin. Uncentrifuged urine contained an occasional red cell, 50 white cells, an occasional hyaline cast and many bacteria per high-power field. The blood showed a red-cell count of 3,000,000, with 9.5 gm. of hemoglobin, and a white-cell count of 23,000, with 92 per cent neutrophils, mostly band forms. The red cells and platelets appeared normal. The stool was normal and guaiac negative. The Hinton test was negative.

X-ray examinations of the chest on the first and third days showed no active disease in the lungs. The heart was prominent and rounded in the region of the left ventricle. An electrocardiogram showed a normal rhythm of 120, marked variation in the form of the P waves in the amplitude of the QRS

\*Shute, P. G. Relapse of quartan fever after twelve and twenty-one years. *Lancet* 2:146, 1944.

complexes, PR intervals ranging from 0.16 to 0.23 second, slight left-axis deviation, upright  $T_1$  and  $T_2$ , low upright T waves in Leads 3 and  $CF_2$  and upright T waves in Leads  $CF_4$  and  $CF_6$ . An occasional ventricular complex showed aberrant conduction. The serum nonprotein nitrogen was 42 mg. per 100 cc., the protein 4.2 gm., and the chloride 98 milliequiv. per liter. The fasting blood sugar was 111 mg. per 100 cc. Repeated blood cultures on the first and third hospital days showed a Type 13 pneumococcus.

Small doses of sulfathiazole were given on the first three days. On the third day intravenous penicillin was begun, and 84,000 to 270,000 units were given daily through the eleventh day. On the sixth day a heavy dose of sulfadiazine was begun and continued through the eighteenth day.

The temperature spiked irregularly once or twice daily as high as 103 to 106°F., not becoming normal or subnormal until the fourth day. The following three days showed a continued fever above 102°F. On the eighth day the temperature, pulse and respiration became normal. Blood cultures taken on the fifth day and after were negative. Because of the unexplained bacteremia associated with mental clouding a lumbar puncture was performed on the fifth day. The initial pressure was normal; the fluid was imperfectly transparent and contained 392 cells per cubic millimeter, almost all of which were polymorphonuclear cells. No bacteria were seen by smears, but the culture grew a beta-hemolytic streptococcus. There were no signs or symptoms of meningitis. Twenty-four thousand units of penicillin were instilled intrathecally. On the following day the spinal-fluid cell count had risen to 2750, with about 80 per cent polymorphonuclear cells. The culture was negative. Thirty to fifty thousand units of penicillin were injected intrathecally in two injections daily for the next five days, during which time there was a gradual reversion of the polymorphonuclear-lymphocyte ratio; the cells finally disappeared on the eleventh hospital day. The urine continued to show an occasional red cell and 5 to 50 white cells per high-power field. Despite eight whole-blood transfusions the red-cell count fell to 2,800,000. The white-cell count after the third day remained about 10,000, with approximately 75 per cent neutrophils.

On the nineteenth hospital day examination of the chest showed dullness in the region of the right lower lobe. Rales were heard over the right scapular region. The heart was enlarged, to a maximum of 11 cm. to the left of the midsternum. A systolic apical thrill was easily felt. The sounds were regular but of poor quality. A harsh Grade 4 systolic murmur was heard all over the lower precordial region, maximal between the apex and lower end of the sternum and best heard near the latter. A mid-diastolic sound was present at the apex. The liver was palpable 5 cm. below the right costal margin.

The tip of the spleen was firm and palpable 2 cm. below the left costal margin. There was slight pitting edema of the sacrum. An electrocardiogram taken at that time showed normal rhythm at 100, a PR interval of 0.23 second, slight left-axis deviation, a low upright  $T_1$ , normal  $T_2$  and  $T_3$ , a low upright T wave in Lead  $CF_2$ , a notched T wave in Lead  $CF_4$  and a normal T wave in Lead  $CF_6$ , with sagging ST segments in Lead  $CF_6$ . An x-ray examination of the left os calcis showed some new-bone formation, with evidence of sequestration. The ulcer had a slight discharge at that time. An intravenous pyelogram was normal. The bladder appeared to be small and quite irregular in outline, especially at the roof, where there was a suggestion of a bilateral filling defect. A gastrointestinal series and barium enema were negative. The spleen appeared enlarged. A repeat x-ray film of the chest showed the heart to be enlarged without a characteristic configuration. There was apparently a considerable amount of fluid in the right pleural cavity, and a small amount in the left. The pulmonary markings were increased.

During the seventh and tenth weeks there were sudden chills followed by fever that spiked irregularly to 104°F. for periods of one to four days and then returned to normal. During these periods the blood cultures were negative. Shortly after the chill in the tenth week a periurethral abscess was found. This drained spontaneously, with remission of the fever. A suprapubic cystostomy was performed. Cultures of the abscess yielded colon bacilli and a nonhemolytic streptococcus. The non-protein nitrogen was 25 mg. per 100 cc., the phosphorus 3.7 mg., the alkaline phosphatase 6.3 units and the acid phosphatase 0.8 units. A Congo red test was negative. Cultures from the draining left heel showed an anaerobic *Staphylococcus albus*. Despite vigorous treatment with iron, liver, diet and transfusions, the anemia progressed, and by the eleventh week the red-cell count had fallen to 2,100,000.

During the twelfth week the suprapubic cystostomy wound failed to heal and reopened spontaneously. Shortly thereafter the temperature rose to 104°F.; the patient became comatose and expired two days later.

#### DIFFERENTIAL DIAGNOSIS

DR. REED HARWOOD: I should like to ask first what the urine cultures showed on the two admissions.

DR. BENJAMIN CASTLEMAN: *Staph. albus* on the first admission, and colon bacilli on the second.

DR. HARWOOD: The neurologic findings represent a typical example of Brown-Séquard syndrome, with the lesion on the right side in the region of the seventh dorsal segment. The patient had weakness and diminished vibration sense on the side of the lesion, and diminished pain and temperature sense

on the contralateral side, owing to the fact that the fibers carrying pain and temperature sense cross immediately in the cord and ascend in the ventral and lateral spinothalamic tracts of the other side. The fact that the neurologic lesion improved in the succeeding two years suggests that the diagnosis of infarct was the correct one.

The record states that hemolytic streptococci were recovered in one culture of the spinal fluid. Considering the large doses of penicillin and sulfadiazine that the patient had received and the fact that a Type 13 pneumococcus was found several times in the blood cultures, I am inclined to believe that the streptococcus in the spinal-fluid culture was a contaminant.

We must now consider the nature of this patient's heart disease. We are told that the heart was normal on the first admission. I think that we must accept this statement and thereby exclude congenital heart disease and old rheumatic valvular disease. There is no mention of arteriosclerosis or hypertension, so that heart disease due to either of these conditions seems unlikely. The electrocardiogram presents no diagnostic abnormality. The changing PR interval suggests some interference with conduction in the auriculoventricular bundle. Dr. White, would you care to comment on that?

DR. PAUL D. WHITE: With a rate of 120, the heart must have been quite irritable to have had so much variation in the P waves. I should think that you were quite right about the possible importance of the variation in auriculoventricular conduction. Whether that should be ascribed to myocardial involvement or to other factors, such as a digitalis effect, is difficult to say on this record alone, although it might have been due to either or to both. The electrocardiogram is certainly not typical of acute myocardial infarction. Had the patient had digitalis?

DR. CASTLEMAN: There is no mention of it.

DR. HARWOOD: The most striking feature of this case is the development of evidence of heart disease. On the first admission the heart was said to be normal. On the second admission, an apical systolic and an early diastolic murmur were noted. Later, in the final illness, the character of this murmur changed: it became much louder and was accompanied by a thrill, and its location appeared to be in the region of the tricuspid valve rather than at the apex. These changes are extremely suggestive of bacterial endocarditis. The character of the fever, the progressive anemia, the bacteremia and the enlarged spleen are all consistent with this diagnosis. The evidence of embolic phenomena is not too positive. Changes in the x-ray films of the chest and in the physical findings in the lungs can be construed as being due to emboli from the right side of the heart. The enlarged spleen and the cloudy spinal

fluid suggest septic emboli from the left side of the heart. But the diagnosis of bacterial endocarditis really rests on the remarkable change in the character of the heart murmurs. I am unable to explain the enlargement of the heart and the changes in the electrocardiogram. It may be that he had a toxic myocarditis; or there may have been multiple small abscesses in the myocardium.

The final question is, Did he have bacterial endocarditis two years before his death, or did he develop an acute endocarditis as a result of the debility resulting from his chronic urinary sepsis? In favor of the former diagnosis are, first, the otherwise unexplained infarct of the spinal cord and, second, the chronic anemia, which was present even at the time of his first admission. On the other hand I must admit that he remained remarkably well during the interim of eighteen months before the acute illness appeared. I should like to make a single diagnosis and so I shall say that he had a subacute bacterial endocarditis.

DR. CASTLEMAN: Dr. Ayer, have you anything to add?

DR. JAMES B. AYER: I saw this man only on the admission two years before his death. He presented evidence of a partial transverse lesion of the spinal cord, which, as you have heard, remained permanently as a Brown-Séquard palsy. The immediate question concerned the possibility of epidural abscess, but the evidence for this was lacking. My opinion was that he suffered from a myelitis, which occasionally occurs in the presence of infection elsewhere and may be due to emboli. There was, however, no evidence of infection in the spinal cord or its meninges.

DR. WHITE: I saw the patient early in February, three weeks before he died, because of the development of this striking murmur. There was a Grade 4 murmur with a thrill. Both murmur and thrill were maximal just to the left of the sternum and not at the apex and resembled Roger's murmur and thrill. But in our analysis we believed, or at least I did, that an acquired ventricular septal defect, because of its great rarity, was less likely than mitral-valve involvement with a torn cusp or chordae tendineae resulting from bacterial endocarditis, which had been helped temporarily by the specific chemotherapy. The third sound could be explained by the delayed auriculoventricular conduction with a long PR interval.

#### CLINICAL DIAGNOSIS

Subacute bacterial endocarditis, with probable rupture of mitral leaflet.

#### DR. HARWOOD'S DIAGNOSES

Subacute bacterial endocarditis (Type 13 pneumococcus).

Chronic cystitis and pyelonephritis.

## ANATOMICAL DIAGNOSES

Acute bacterial endocarditis, posterior aspect of mitral valve, with perforation into right auricle (Type 13 pneumococcus).

Acute and chronic pyelonephritis, urethritis, prostatitis and cystitis.

## PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The heart was only slightly enlarged, weighing 400 gm. Just below the aortic valve, between the left posterior and the anterior

to have arisen on that side of the heart. There was no evidence of previous disease on any of the valves. Microscopically the vegetation was fairly acute. It was made up almost entirely of polymorphonuclear cells and organisms that on culture proved to be Type 13 pneumococci. He had, of course, infection in the kidneys, urethra, prostate and bladder.

Before discussing whether the bacterial endocarditis could have been connected with the cord symptoms of almost two years previously, Dr. Kubik will tell us what he found in the cord.



FIGURE 1. Photograph of the Heart Showing the Ulcerated Vegetation below the Aortic Valve.

cusps but not involving either cusp and actually on the posterior aspect and within the wall of the aortic leaflet of the mitral valve, was a large granular pinkish-red ulcerating vegetation (Fig. 1). This obvious bacterial endocarditis did not penetrate through the endocardium of the anterior surface of the mitral leaflet into the left auricle but faced the left ventricle. It did, however, perforate through at its right border into the right auricle just above the tricuspid valve (Fig. 2). It extended only a bit onto the tricuspid valve, and it did not appear

DR. CHARLES S. KUBIK. I saw this patient on his last admission and said at that time that, although infarction or any other type of vascular lesion of the cord was extremely rare, it was suggested in this case by the sudden onset of symptoms and the subsequent improvement. I suppose that vascular lesions of the cord are rare because the cord has a good collateral circulation.

At autopsy there was a localized focus of degeneration in the anterior part of the cord at about the sixth thoracic level. The histologic appearance of

this lesion was consistent with old infarction, but one probably cannot be altogether certain of the diagnosis. In any case, because of the time relations, it cannot be satisfactorily explained by the acute bacterial endocarditis.

defect, but the murmur was absolutely characteristic of the latter.

DR. CASTLEMAN: Do you think that the perforation in the right auricle, rather than into the ventricle as is usual in septal defect, might have had



FIGURE 2. *Photograph of the Heart Showing the Perforation of the Right Auricle.*

DR. WHITE: May I add a comment about the murmur. It was so characteristic of Roger's murmur that we should have stuck to our auscultatory diagnosis of a ventricular septal defect. Because of the rarity of an acquired septal defect in such a case I voted for mitral valve rupture rather than septal

something to do with the change in the murmur?

DR. WHITE: I believe that one should find the same type of murmur with a defect leading from ventricle to auricle that one would find in the case of a hole between the ventricles. The flow of blood is much the same.



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## PULP PRESERVATION

ONE of the many difficulties besetting a journal editor in these grueling days, although only one of them, is that brought about by the current paper shortage. This is largely due, as are so many of our internal problems, to the lack of manpower, but it has also other more acute angles, although some of these too are indirectly the result of labor difficulties. Thus since steel is a critical material with high priority rating, there exists a shortage of axheads and sawblades. Without axheads and without lumbermen to cut the wood for axhandles, a shortage in the latter becomes obvious, still further embarrassing pulp production. It seems hardly

necessary to mention shortages of farm help, so necessary to raise the beans on which lumbermen are reputedly fed.

Various methods have been employed to conserve our depleted supply of paper. The *Journal*, for instance, having been sharply curtailed in its annual paper allotment, has had to stretch that allotment by the use of a lighter weight paper, by reducing the number of pages, despite an unusually good supply of excellent material for publication and the demands of our advertisers for more space, and by limiting the allowable number of reprints.

Printers have had their purchases of paper cut to a prescribed percentage of normal consumption as of a given year, according to regulations issued and sent to each one in the form of a governmental pamphlet containing as a part of its message, we have been told, five printed lines on page 4, three lines on page 5, and nothing on pages 6, 7 and 8. (These may have been left blank for remarks!)

One of the most serious problems that these curtailments have raised, however, has been their contribution to the shortage of waste paper. The uses of waste paper have been graphically illustrated; it is going overseas on a variety of missions, — as wrapping for artillery shells, jeep fenders, small-arms ammunition, bazookas, machine-gun triggers and K rations, — but the supply is dwindling. There seemed for a time no solution to this problem, but it has been inspiringly met.

Government itself has gone into the production of waste paper. By using eight pages where four would have sufficed, by tripling its regulations and doubling the number of words in each, by requiring fifty-six signatures where six would have served and by specifying quintuplicate instead of triplicate copies of declarations, questionnaires and directives, the emergency has been met. The war can go on!

## ETIOLOGY OF EXUDATIVE PHARYNGITIS

MOST, if not all, clinicians have the impression that acute pharyngitis and acute tonsillitis are always caused by hemolytic streptococci. This is particularly true with respect to the cases that are associated either with a purulent follicular exudate or

with a fine pseudomembranous exudate. In recent years, however, many physicians interested in infectious diseases and others working on the medical wards of general hospitals where bacteriologic studies are made routinely have been surprised to find that many, or even the majority, of the seemingly typical cases of pharyngitis and tonsillitis — excluding, of course, cases of scarlet fever and septic sore throat — failed to yield positive cultures of beta-hemolytic streptococci.

In the course of the studies that are being conducted by the Commission on Acute Respiratory Diseases at Fort Bragg, about 10 per cent of the patients admitted to the hospital for acute respiratory diseases were found to have exudate on the pharynx or tonsils. Some of those patients had both bacteriologic and clinical evidence of hemolytic streptococcus pharyngitis; others had positive throat cultures, but the clinical picture was not entirely characteristic; and still others had neither cultural nor characteristic clinical findings of hemolytic streptococcus infections. The members of the commission\* therefore undertook a systematic clinical and laboratory study of the problem. They believed that, since beta-hemolytic streptococci are harbored in the throats of healthy persons as well as in those of patients suffering from colds and other respiratory infections, the diagnosis of streptococcal pharyngitis could be made with certainty only if a specific antibody response was demonstrated against that organism during convalescence. Thus, samples of serum obtained during the acute febrile stage of the illness and again during convalescence were tested for their antistreptolysin titer in each case.

The patients under investigation were routine admissions for acute respiratory symptoms who came to the hospital from selected organizations of that post. The criterion for admission was simply the finding of a temperature of 100°F. or higher when the men reported to the dispensary. Of 900 men admitted during the period of study, 116 were found to have exudate on the pharynx or tonsils and were selected for the study.

On the basis of the laboratory data the cases were classified into three groups. The first group com-

prised approximately 25 per cent of the cases and included those in which beta-hemolytic streptococci were obtained in the cultures and in which a significant rise in the titer of streptococcal antibodies developed during convalescence. The second group consisted of another 25 per cent of the patients; these men had positive cultures for hemolytic streptococci but did not develop antibodies during convalescence. The last group, which consisted of the remaining 50 per cent of the patients, had neither positive cultures for beta-hemolytic streptococci nor rises in titer of antistreptolysin. Definite differences were demonstrated between the cases with and those without antibodies regarding the mode and rapidity of onset, the total frequency of symptoms, the severity of the physical findings and the height of the white-cell count. Cases with beta-hemolytic streptococci in which antibodies did not develop were similar in their clinical characteristics to those in which streptococci were not found.

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\*Commission on Acute Respiratory Diseases. Endemic exudative pharyngitis and tonsillitis: etiologic and clinical characteristics. *J. A. M. A.* 125: 1163-1169, 1944.

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## PULP PRESERVATION

ONE of the many difficulties besetting a journal editor in these grueling days, although only one of them, is that brought about by the current paper shortage. This is largely due, as are so many of our internal problems, to the lack of manpower, but it has also other more acute angles, although some of these too are indirectly the result of labor difficulties. Thus since steel is a critical material with high priority rating, there exists a shortage of axheads and sawblades. Without axheads and without lumbermen to cut the wood for axhandles, a shortage in the latter becomes obvious, still further embarrassing pulp production. It seems hardly

necessary to mention shortages of farm help, so necessary to raise the beans on which lumbermen are reputedly fed.

Various methods have been employed to conserve our depleted supply of paper. The *Journal*, for instance, having been sharply curtailed in its annual paper allotment, has had to stretch that allotment by the use of a lighter weight paper, by reducing the number of pages, despite an unusually good supply of excellent material for publication and the demands of our advertisers for more space, and by limiting the allowable number of reprints.

Printers have had their purchases of paper cut to a prescribed percentage of normal consumption as of a given year, according to regulations issued and sent to each one in the form of a governmental pamphlet containing as a part of its message, we have been told, five printed lines on page 4, three lines on page 5, and nothing on pages 6, 7 and 8. (These may have been left blank for remarks!)

One of the most serious problems that these curtailments have raised, however, has been their contribution to the shortage of waste paper. The uses of waste paper have been graphically illustrated; it is going overseas on a variety of missions, — as wrapping for artillery shells, jeep fenders, small-arms ammunition, bazookas, machine-gun triggers and K rations, — but the supply is dwindling. There seemed for a time no solution to this problem, but it has been inspiringly met.

Government itself has gone into the production of waste paper. By using eight pages where four would have sufficed, by tripling its regulations and doubling the number of words in each, by requiring fifty-six signatures where six would have served and by specifying quintuplicate instead of triplicate copies of declarations, questionnaires and directives, the emergency has been met. The war can go on!

## ETIOLOGY OF EXUDATIVE PHARYNGITIS

MOST, if not all, clinicians have the impression that acute pharyngitis and acute tonsillitis are always caused by hemolytic streptococci. This is particularly true with respect to the cases that are associated either with a purulent follicular exudate or

with a fine pseudomembranous exudate. In recent years, however, many physicians interested in infectious diseases and others working on the medical wards of general hospitals where bacteriologic studies are made routinely have been surprised to find that many, or even the majority, of the seemingly typical cases of pharyngitis and tonsillitis — excluding, of course, cases of scarlet fever and septic sore throat — failed to yield positive cultures of beta-hemolytic streptococci.

In the course of the studies that are being conducted by the Commission on Acute Respiratory Diseases at Fort Bragg, about 10 per cent of the patients admitted to the hospital for acute respiratory diseases were found to have exudate on the pharynx or tonsils. Some of those patients had both bacteriologic and clinical evidence of hemolytic streptococcus pharyngitis; others had positive throat cultures, but the clinical picture was not entirely characteristic; and still others had neither cultural nor characteristic clinical findings of hemolytic streptococcus infections. The members of the commission\* therefore undertook a systematic clinical and laboratory study of the problem. They believed that, since beta-hemolytic streptococci are harbored in the throats of healthy persons as well as in those of patients suffering from colds and other respiratory infections, the diagnosis of streptococcal pharyngitis could be made with certainty only if a specific antibody response was demonstrated against that organism during convalescence. Thus, samples of serum obtained during the acute febrile stage of the illness and again during convalescence were tested for their antistreptolysin titer in each case.

The patients under investigation were routine admissions for acute respiratory symptoms who came to the hospital from selected organizations of that post. The criterion for admission was simply the finding of a temperature of 100°F. or higher when the men reported to the dispensary. Of 900 men admitted during the period of study, 116 were found to have exudate on the pharynx or tonsils and were selected for the study.

On the basis of the laboratory data the cases were classified into three groups. The first group com-

prised approximately 25 per cent of the cases and included those in which beta-hemolytic streptococci were obtained in the cultures and in which a significant rise in the titer of streptococcal antibodies developed during convalescence. The second group consisted of another 25 per cent of the patients; these men had positive cultures for hemolytic streptococci but did not develop antibodies during convalescence. The last group, which consisted of the remaining 50 per cent of the patients, had neither positive cultures for beta-hemolytic streptococci nor rises in titer of antistreptolysin. Definite differences were demonstrated between the cases with and those without antibodies regarding the mode and rapidity of onset, the total frequency of symptoms, the severity of the physical findings and the height of the white-cell count. Cases with beta-hemolytic streptococci in which antibodies did not develop were similar in their clinical characteristics to those in which streptococci were not found.

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*Personality and the Behavior Disorders: A handbook based on experimental and clinical research.* In two volumes. Edited by J. McV. Hunt, Ph.D., assistant professor of psychology, Brown University. 8°, cloth: Vol. 1, 618 pp., and Vol. 2, 624 pp. New York: The Ronald Press Company, 1944. \$10.00 for the set.

This collective treatise is the work of thirty-five experts who have reviewed the present knowledge of personality in the biologic, psychologic and psychiatric aspects of the subject. Extensive bibliographies have been appended to each article and complete indices of names and subjects have been appended to the text. The work should prove of value as a reference source for psychiatrists, psychologists and sociologists, and also should find a place in every medical and reference library.

*Essays in Biology: In honor of Herbert M. Evans.* Written by his friends. 4°, cloth, 686 pp., illustrated. Berkeley: University of California Press, 1943. \$10.00.

This memorial volume was presented to Dr. Evans on his sixtieth birthday by his colleagues, his students and other friends. Dr. Evans is professor of anatomy, Hertzstein Professor of Biology and director of the Institute of Experimental Biology in the University of California. He has devoted his life to the fundamental problems of anatomy, embryology, endocrinology and nutrition and the physiology of reproduction. He also has been interested in the history of science and medicine in all their aspects. In this volume there are forty-eight papers written by his friends on the various subjects with which he is concerned. At the beginning of the volume there is a complete bibliography of the writings of Dr. Evans.

*The Jews and Medicine: Essays.* In two volumes. By Harry Friedenwald, M.D., D.H.L. (hon.), D.Sc. (hon.). 8°, cloth: Vol. 1, 390 pp., with 25 illustrations and frontispiece, and Vol. 2, 427 pp., with 13 illustrations. Baltimore: The Johns Hopkins Press, 1944. \$3.75 (for each volume).

Dr. Friedenwald has been interested in the history of Jewish physicians and the contributions of Jews to medicine for almost half a century. During this period he has written many articles and essays of a biographical and historical character, which are brought together in these two volumes. Coincidentally with his interest in Jewish literature and medicine, Dr. Friedenwald has made a fine collection of manuscripts and early printed books in these fields. Dr. Henry E. Sigerist, in the preface, discusses the medical collectors of Baltimore, especially those connected with Johns Hopkins University School of Medicine and particularly Dr. Friedenwald and his collection of medical classics of the Jews.

*A Text-Book of Pathology.* Edited by E. T. Bell, M.D., professor of pathology, University of Minnesota, Minneapolis. Fifth edition, enlarged and thoroughly revised. 8°, cloth, 862 pp., with 448 illustrations and 4 colored plates. Philadelphia: Lea and Febiger, 1944. \$9.50.

The greater part of the text has been thoroughly revised and a large amount of new material has been added. Among the new topics discussed at length are shock, vitamin deficiencies, blast injuries, Boeck's sarcoid and several infectious diseases of interest in war medicine. The work is primarily a textbook for the medical student to use during his clinical training.

*Medical Care of the Discharged Hospital Patient.* By Frode Jensen, M.D., instructor in medicine, Syracuse University College of Medicine; H. G. Weiskotten, M.D., dean and professor of pathology, Syracuse University College of Medicine; and Margaret A. Thomas, M.A. (Oxon). 8°, cloth, 80 pp. New York: The Commonwealth Fund, 1944. \$1.00.

This is a report of a successful experiment in extending the range of a hospital service, thus improving the care of chronically ill patients and relieving congestion in the medical wards. The study was carried out in the University Hospital of the University of Syracuse College of Medicine. A special extra-mural resident was assigned to the task of familiarizing himself with the medical aspects of chronic cases and their relevant emotional, social and economic factors. He also investigated the facilities for home treatment and was authorized to continue the medical supervision of the patients in their homes

after discharge. It was found that, because of proper facilities for care in the home, many patients could be discharged earlier and rehospitalization was greatly reduced. Sufficient hospital facilities were released to permit the acceptance of several hundred patients. The information revealed by this experience re-emphasizes the fact that the hospital is the pivot around which should revolve the various services: hospital care, outpatient care and public-welfare programs. The provision of adequate home care for discharged medically needy patients is a step toward a more economical and beneficial use of the hospital in the care of the indigent. This small monograph should be of interest to all hospital administrators as well as to physicians having to do with chronic illness.

*Applied Dietetics: The planning and teaching of normal and therapeutic diets.* By Frances Stern, chief of Frances Stern Food Clinic, Boston Dispensary, assistant in medicine, Tufts College Medical School, special instructor in dietetics in social service and associate in nutrition, Simmons College, Boston. Second edition. 4°, cloth, 265 pp., with 57 tables. Baltimore: The Williams and Wilkins Company, 1943. \$4.00.

This is a revised edition of a book first printed in 1936. The work is based on the methods developed in the food clinic of the Boston Dispensary, the pioneer clinic of its kind, organized twenty-five years ago. It has been revised to include the information on nutrition developed during the seven years that have elapsed since the publication of the first edition. The section on the vitamins has been rewritten to conform to the latest chemical knowledge of these elements. The bulk of the information is presented in tabular form. There are fifty-seven co-ordinated tables to simplify the computation of the diet, and there are twenty pairs of full-page tables setting out in detail typical menus and diets. A normal diet is considered in relation to normal physiology, whereas the therapeutic diet is treated as a deviation from the normal, calling for an increase or decrease in the amount of a food constituent, or the omission or change in the consistence of foods as used in the normal diet.

*Sulfonamide Therapy in Medical Practice.* By Frederick C. Smith, M.D., M.Sc., lieutenant colonel, Medical Reserve Corps, Army of the United States. With a foreword by George M. Piersol, B.S., M.D., professor of medicine, Graduate School of Medicine, University of Pennsylvania. 8°, cloth, 368 pp., with illustrations, tables and charts. Philadelphia: F. A. Davis Company, 1944. \$5.00.

This new manual has been written to point out the possibilities of sulfonamides in treatment and to emphasize their limitation and their toxic properties. The first 94 pages discuss pharmacology and therapeutics, toxic reactions and tests. The remaining portion of the work is devoted to clinical indications for sulfonamide therapy and is arranged alphabetically by diseases. An appendix of 12 pages discusses penicillin. Current literature has been utilized and a number of illustrative cases have been included in the text. This timely manual should prove of interest to all physicians who may wish to refer to the use of sulfa drugs in various infections.

*Medical Physics.* Edited by Otto Glasser, Ph.D., head, Department of Biophysics, Cleveland Clinic Foundation, professor of biophysics, Frank E. Bunts Educational Institute, and consulting biophysicist, University Hospitals of Cleveland. 4°, paper, 1744 pp., illustrated. Chicago: The Year Book Publishers, Incorporated, 1944. \$18.00.

This outstanding encyclopedia, with signed contributions by over two hundred authorities in various fields of biology and medicine, should prove to be a valuable reference book for all libraries and for all physicians who are brought into contact with medical physics in any of its varying aspects, as well as radiologists and biologists. The articles are arranged alphabetically by subject, but there are classified tables of contents preceding the text that show at a glance all the articles in the various fields of medicine and physics. Many of the authors have attached good working bibliographies to their contributions. The book is well illustrated, printed in a good type on good paper, but is rather unwieldy to handle because of its size and weight. Comprehensive subject and name indices are appended to the text.

(Notices on page xix)

# The New England Journal of Medicine

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## TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH PENICILLIN\*

MANSON MEADS, M.D.,† H. WILLIAM HARRIS, M.D.,‡ AND MAXWELL FINLAND, M.D.§

WITH THE TECHNICAL ASSISTANCE OF CLARE WILCOX

BOSTON

ALTHOUGH the sulfonamide drugs are highly effective in the treatment of the pneumococcal pneumonias, serious problems sometimes arise in their administration. In patients with underlying cardiac or renal disease there may be considerable difficulty in maintaining proper fluid balance and in preventing urinary-tract complications while the drugs are being given in adequate doses. Some of the toxic effects of the sulfonamides may not only be dangerous in themselves but may make it necessary to discontinue this therapy before the infection is adequately controlled. Moreover, occasional cases apparently fail to respond to treatment with adequate doses, either because the organism is not susceptible or for other reasons.

Penicillin, on the other hand, seems to be free from many of these difficulties and at the same time is extremely effective against the pneumococcus. In-vitro tests have shown that pneumococci are highly susceptible to penicillin.<sup>1-6</sup> This has been confirmed in the treatment of experimental infections in mice<sup>7,8</sup> and in chick embryos.<sup>9</sup> Resistant strains from clinical cases have not been reported, although strains have been made resistant in vitro<sup>10</sup> and by serial passage through mice treated with subeffective doses of the agent.<sup>11</sup> Both sulfonamide-sensitive and sulfonamide-resistant strains seem to be equally susceptible to the action of penicillin.<sup>12,13</sup>

Tillett, Cambier and McCormack<sup>14</sup> report excellent results in the treatment of 46 cases of lobar pneumonia with penicillin. These cases were mostly of pneumococcal etiology and were of average severity. Others<sup>15,16</sup> reporting miscellaneous groups of infections treated with penicillin have included

small numbers of cases of pneumococcal pneumonia in which similar results were obtained.

It is the purpose of this paper to report the results of treatment with penicillin in a series of 54 rather severe cases of pneumococcal pneumonia. Penicillin was used alone in 37 of these cases, whereas in the remaining 17 cases it was given only after sulfonamide drugs had either failed to bring about a satisfactory response or produced untoward effects that made it undesirable to continue their use, although the patients were still acutely ill.

### MATERIAL AND METHODS

#### *Selection of Cases*

All the patients had pneumococcal pneumonia and were admitted to one of the medical services of the Boston City Hospital from March through December, 1944. The 37 patients who were treated with penicillin alone (Group I) had not previously received sulfonamides for this illness. This was determined from the history and confirmed, when there was any doubt, by the failure to find any sulfonamide in the blood taken on admission. All these patients had pneumococci that were readily typed directly from the sputum by the Neufeld method at the time of entry. Sulfonamides or specific antisera were not used during the penicillin treatment in these cases.

The remaining 17 patients (Group II) had received sulfonamides, usually in full doses, before the penicillin was started, and the change to the latter was made for one or more of the following reasons. In most cases, the clinical condition became worse. In 1 such case the penicillin was begun after fourteen hours on sulfonamides, and in 10 others after more than thirty hours. In 2 cases, peripheral vascular collapse or congestive failure developed. In 7 cases, there was clinical evidence of a spread of the pulmonary lesion after thirty hours or more on sulfonamides. In 5 cases, positive blood cultures were obtained thirty-six hours or more after sulfonamides were started. In 1 case, there was persistence of

\*From the First, Second and Fourth Medical Services and the Department of Medicine, Harvard Medical School.

†The penicillin used in this study was provided, in part, by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

‡Research fellow in Medicine, Harvard Medical School and Thorndike Memorial Laboratory.

§Research fellow, Thorndike Memorial Laboratory.

¶Assistant professor of medicine, Harvard Medical School; chief, Fourth Medical Service, and associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

marked toxemia and leukopenia. In 2 cases, the patients were in extremis on entry after receiving undetermined amounts of sulfonamides. In 1 case, there were severe renal complications of sulfonamide therapy. Other factors that influenced the decision to change to penicillin included the advanced age of the patient, elevation of the blood nonprotein nitrogen and severe underlying disease or prolonged sulfonamide therapy without adequate improvement.

Some of the salient features of all the cases are summarized in Table 1. On the whole, they repre-

TABLE 1. Summary of Data.

DATA	GROUP I PENICILLIN	GROUP II PENICILLIN AFTER SULFONAMIDE
Total cases	37	17
Male	32	14
Female	5	3
Age of patient:		
Under 40 years	12	5
40-59 years	16	10
60 years and over	9	2
Duration before penicillin:		
Less than 2 days	4	0
2 or 3 days	8	1
4-6 days	14	10
7 days or more	11	5
Unknown	0	1
Number of lobes involved:		
One	16	2
Two or three (unilateral)	12	11
Two or three (bilateral)	9	5
Severity before penicillin:		
Grade 2 (moderately ill)	15	1
Grade 3 (acutely ill and irrational)	9	5
Grade 4 (shock or congestive failure, or both)	13	11
Pneumococcal types:		
Common types (1, 2, 3, 4, 5, 7 and 8)	28	11
Higher types (all others)	9	6
Bacteremia	19	10
Leukocyte count:		
Less than 5000	6	5
5000-10,000	4	1
11,000-30,000	23	10
More than 30,000	4	1
Chronic alcoholism (total cases)*	10	7
With delirium tremens	4	2
With cirrhosis of liver	2	2
Deaths	7	3

\*Other complicating conditions — Group I: bronchiectasis, 2 cases; sickle-cell anemia, 1 case; aplastic anemia, 1 case; empyema on admission, 2 cases. Group II: bronchiectasis, 1 case; moderately advanced pulmonary tuberculosis, 1 case; chronic pyelonephritis, 2 cases; arteriosclerotic heart disease, 4 cases (1 with angina and 1 with asthma).

sented severe cases by all the usual criteria. More than two thirds of the patients were over forty years old. Penicillin was started in most cases after the fourth day of the disease. The majority had two or more lobes involved and appeared clinically to be severely ill, with delirium, evidence of peripheral vascular collapse — cold clammy skin, cyanosis and low blood pressure — or congestive failure. More than half the patients had positive blood cultures. The pneumococci were predominantly of the lower or so-called "common" types, but there were 2 cases in each group in which a higher type of pneumococcus was grown from the blood. A few patients had either leukopenia or extremely high white-cell counts before penicillin treatment was started. Several patients had severe underlying diseases, and in 2 cases there were signs of fluid at the time of entry. Judging from these findings, the cases in Group II were somewhat severer than those in Group I.

## Methods

At the time of admission, sputum was obtained for typing by the Neufeld technic and venous blood was obtained for cultures in broth and agar and, in many cases, for sulfonamide determinations. Some of the sputum was also cultured and the pneumococcus strains were isolated. Additional blood cultures were made at irregular intervals after penicillin was started. In the Group II cases, a culture and sulfonamide determination of the blood were made before the first dose of penicillin. Para-aminobenzoic acid was added to all mediums used for cultures in cases under sulfonamide therapy, and penicillinase\* was added in most of the cultures made during penicillin treatment.

In most cases, the pneumococcus strains isolated from the sputum or blood were tested for sensitivity to penicillin by the method of Rammelkamp and Maxon.<sup>17</sup> Concentrations of penicillin in the blood were determined by the method of Rammelkamp.<sup>18</sup>

## Penicillin Administration and Dosage

On the whole, the dosage was individualized with respect to the amount and frequency of the injections and the total duration of treatment. The severity of the disease, the clinical response and the concentrations obtained in the blood were all taken into account. Difficulties were encountered in properly maintaining the constant intravenous injections, particularly in the types of case in which that method seemed most indicated. Intermittent intramuscular administration was the most feasible method and was therefore generally used.

Most of the patients classified as Grade 2 or 3 in severity were given from two to six injections of 15,000 units every two hours, and the same amount was given every three hours until there was definite clinical improvement and the temperature had remained below 100°F. for twelve hours. Additional doses of 10,000 units each were then given every three hours for another two or three days. In the severest cases (Grade 4), the same general scheme of dosage was used except that a single dose of 5000 or 10,000 units was given intravenously in some cases at the time of the first intramuscular injection and from six to twelve injections of 15,000 units were given at two-hour intervals, depending on the response of the patient during that time. In most patients with congestive failure or in those with a low urinary output from this or other causes, bacteriostatic levels were usually maintained for somewhat longer periods than in other patients after similar doses. In such cases the interval between doses could therefore be increased.

The average total dose and duration of treatment in each of the various groups of recovered cases are shown in Table 2. The dosages are considerably larger than those used by Tillett et al.<sup>14</sup> but they

\*Kindly supplied by Drs. H. J. White and R. O. Roblin, Jr., of the Stamford Laboratories, Stamford, Connecticut.

were not deemed excessive in view of the severity of these cases and the clinical response observed. In the present series, the average dose and duration

TABLE 2. *Average Total Dosage of Penicillin and Duration of Treatment in Recovered Cases.*

TYPE OF CASE	AVERAGE TOTAL DOSAGE OF PENICILLIN units	AVERAGE DURATION OF TREATMENT hr.
Group I	411,000	86
Group II	728,000	162
Severity:		
Grade 2	317,000	66
Grade 3	477,000	107
Grade 4	735,000	148
All cases	507,000	107

of treatment were directly proportional to the severity of the disease.

### Other Therapy

Supportive and symptomatic therapy, including proper hydration, the use of oxygen, digitalis, sedation and stimulants, was used as indicated. Inadequate attention to some of these details may have contributed to the failures in single cases. The need for a large fluid intake, which is so essential in sulfonamide-treated cases to avoid renal complications, was obviated with the use of penicillin. This was particularly helpful in some of the patients with congestive failure.

## RESULTS

### Effect on the Clinical Course

The effect on the clinical course may be judged from the duration of fever and of acute symptoms, such as delirium, prostration and dyspnea, after the penicillin was started. These results are summarized in Table 3. About half the patients were

TABLE 3. *Duration of Fever and Acute Symptoms after First Dose of Penicillin in Recovered Cases.*

DATA	GROUP I CASES	GROUP II CASES	ALL CASES
Duration of fever (100°F. or higher):			
12 hours or less	9	4*	13
13-24 hours	7	2	7
25-36 hours	5	1	8
37-48 hours	3	1	4
More than 48 hours	6†	6	12
Duration of acute symptoms:			
12 hours or less	7	0	7
13-24 hours	14	5	19
25-36 hours	5	1	6
37-48 hours	1	3	4
More than 48 hours	3	5	8

\*Two of these patients were still acutely ill but had no fever when penicillin was started.

†One of these patients (Case 33) did not become afebrile until after penicillin was stopped and a sulfonamide drug was given.

essentially afebrile and markedly improved symptomatically within twenty-four hours, and most of the remaining ones who had not previously been treated with sulfonamides were essentially recovered by the end of the second day. In 10 cases, the fever continued for one to four days after marked clinical

improvement had occurred. In 4 of the Group II cases, on the other hand, symptoms persisted for one to four days after the fever had subsided. In several cases, the persistence of fever and symptoms was associated with active delirium tremens or with the presence of complications. Examples of the clinical course in a few cases are illustrated in Figures 1-7, which show various types of response to penicillin.

### Effect on Bacteremia

The results of blood cultures taken in 18 of the bacteremic cases before treatment and again within the first twenty-four hours after penicillin was started are shown in Table 4. In only 4 cases was a positive blood culture obtained after the penicillin treatment was begun, and in each case only a single dose of 15,000 units had been given two or three hours before the positive culture was obtained. In one of these patients (Case 39), the culture taken after the last dose of sulfonamide and before the first dose of penicillin showed no growth. In all 4 of these cases, the blood culture taken six to twenty hours later was negative. In the remaining 14 cases, all the blood cultures taken after penicillin was started showed no growth. These negative cultures were obtained as early as fifteen minutes after the initial dose of penicillin in 1 case, thirty minutes after the first dose in a second case, and two to four hours after treatment was started in five others.

In the 11 bacteremic cases that are not listed in this table, either the patient died before a second blood culture could be obtained or subsequent cultures were negative but were taken after the patient was already afebrile.

### Complications

It is noteworthy that no purulent complications developed in either group of cases after penicillin treatment was started. There were 2 cases, however, in which empyema was already present before the penicillin was given. One of these patients died two hours after the first dose. The other also had an early purulent arthritis. He was given five intrapleural injections of 10,000 units each, but it was necessary to resort to surgical drainage for cure. The arthritis in this case responded to a single intra-articular injection of 10,000 units of penicillin. In 1 other patient (Case 51), a Type 4 pneumococcus was obtained from both sputum and ascitic fluid at the time of entry. This patient died with congestive failure after two days on penicillin.

Sterile pleural effusions developed in 2 cases of Group I. Partial atelectasis of the resolving lung occurred in 3 cases of Group I and in 2 of Group II. These complications were associated with persistence of a low-grade fever after the acute symptoms subsided.

Relapse of the pneumonia with the same type of pneumococcus but with involvement of another



lobe occurred in Case 3 (Fig. 1). This patient received only 100,000 units of penicillin in ten hours by constant intravenous injection, and the relapse occurred ten days later. A relapse with a pneumococcus of a different type occurred in Case 46. This patient was a seventy-one-year-old woman who was from the sputum. She responded with complete recovery to a second course of 660,000 units of penicillin. A third patient (Case 20), with underlying pyelonephritis, hypertensive heart disease and persistent azotemia, was successfully treated for a Type 18 pneumococcus pneumonia of the left lower

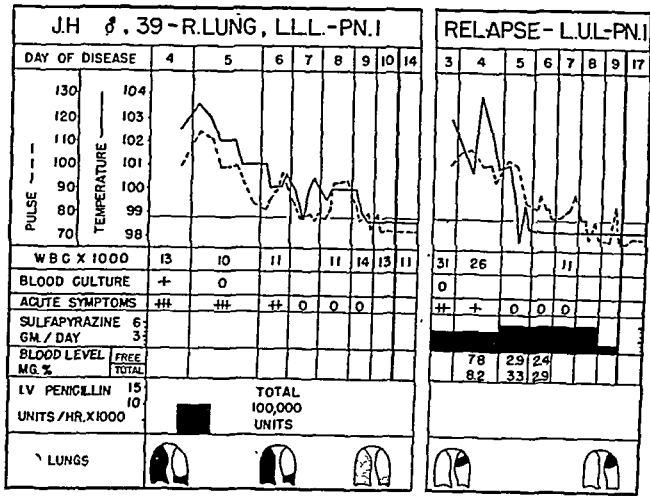


FIGURE 1. Course and Treatment in Case 3.  
In this case the administration of 100,000 units of penicillin by constant intravenous drip over a period of ten hours was followed by slow but steady improvement. The onset of symptoms of relapse occurred on the third day after the patient was discharged. Type 1 pneumococci were found in large numbers in the sputum during both attacks.

first treated for Type 3 pneumococcus pneumonia of the right upper lobe that had failed to respond to sulfadiazine. She improved rapidly after penicillin was started, and she had received a total of 370,000 lobe and again one month later for a Type 3 pneumococcus pneumonia of the right lower lobe. The pneumococcus was obtained each time from blood and sputum.

TABLE 4. Effect of Penicillin Therapy on Bacteremia.

CASE No *	TYPE OF PNEUMO- COCCUS	BLOOD CULTURE BEFORE PENICILLIN TREATMENT			FIRST BLOOD CULTURE AFTER PENICILLIN BEGUN			SECOND BLOOD CULTURE AFTER PENICILLIN BEGUN						
		TIME AFTER SULFON- AMIDE BEGUN hr.	BROTH	BLOOD- AGAR PLATE col./cc.	TIME AFTER FIRST DOSE hr.	DOSAGE OF PENI- CILLIN units	TIME AFTER LAST DOSE hr.	BROTH	BLOOD- AGAR PLATE col./cc.	TIME AFTER FIRST DOSE hr.	DOSAGE OF PENI- CILLIN units	TIME AFTER LAST DOSE hr.	BROTH	BLOOD- AGAR PLATE col./cc.
1	1		+	0	2 ½	30,000	½	0	0	4 ½	45,000	½	0	0
2	1		+	12	9	60,000	2	0	0					
3	1		+	0	13 ½	100,000†	3 ½	0	0	61 ½	100,000	51 ½	0	0
40	1	? 144	+	32	2	15,000	2	+	0	13	75,000	1	0	0
5	2		+	16	8	30,000	2	0	0	54	195,000	3	0	0
17	3		+	0	3	15,000	3	0	0					
27	3		+	33	¾	20,000	¾	0	0	10 ½	125,000	3	0	0
49	3	72	0	1	2	25,000	2	0	0					
8	5		+	480	2	15,000	2	+	0	8	60,000	2	0	0
38	5	144	+	0	2	20,000	2	0	0	17	120,000	1	0	0
43	7	51	+	32	4	12,500	†	0	0	13	80,000	†	0	0
11	7		+	31	3	15,000	3	+	0	11	60,000	3	0	0
18	7		+	416	¾	20,000	¾	0	0	½	20,000	½	0	0
26	7		+	—	12	75,000	2 ½	0	0					
54	7	36	+	2	22	160,000	2	0	0					
33	8		+	500	22	160,000	1	0	0	47	310,000	2	0	0
25	19		+	0	17	105,000	2	0	0					
39	25	38	0	0	2	15,000	2	+	0	22	120,000	2 ½	0	0

\*Cases 1-37 received no sulfonamide (Group I); Cases 38-54 received sulfonamide before penicillin (Group II).  
†Continuous intravenous administration.

units. Three days after this course was completed she again developed fever, respiratory symptoms, leukocytosis and signs of a diffuse bronchopneu- monia and a Type 24 pneumococcus was obtained Thrombophlebitis occurred in 2 cases. In neither of them was penicillin given by the intravenous route. In one of these patients the thrombophlebitis developed on the seventh day after a good clinical

response, but later the patient suddenly died following a femoral-vein ligation. In the other patient, sulfonamides had been used first; a posterior tibial thrombophlebitis developed four days after penicillin was started and subsided after six days.

One patient in Group I developed acute cardiac failure and pulmonary edema and died shortly after treatment was started. Auricular fibrillation occurred in 2 of the Group II cases. In one of them, it commenced twelve hours after penicillin therapy was begun and lasted for twenty-four hours; in the other, it began after twenty-four hours of penicillin therapy and lasted for four days. In both cases, restoration of normal sinus rhythm accompanied

course of 2,000,000 units given over a period of eleven days.

In Case 43, penicillin was started because of the development of anuria and uremia on sulfadiazine. A drug rash developed six days after the sulfonamide was discontinued and the penicillin was started. The blood-sulfadiazine level at that time was 10 mg. per 100 cubic centimeters, 4 mg. of which was in the free form.

### *Untoward Effects of Penicillin*

Except for a mild burning sensation experienced by several patients at the site of some of the intramuscular injections, there were only two complica-

TABLE 5. *Relevant Data in Fatal Cases.*

CASE No.	AGE	TYPE OF PNEUMOCOCCUS	DURATION BEFORE TREATMENT days	INITIAL BLOOD CULTURE	LOBES INVOLVED*	GRADE OF SEVERITY	PENICILLIN THERAPY			COMMENTS
							TOTAL NO. OF INJECTIONS	TOTAL DOSAGE units	TIME FROM FIRST DOSE TO DEATH hr.	
16	57	1	7	0	Lu, Rl(m)	4	5	75,000	8	Chronic alcoholism; peripheral vascular collapse.
17	59	3	? 8	+	Ruml	4	2	30,000	3	Chronic alcoholism; hypertensive heart disease; congestive failure.
18	36	7	? 4	+	Lul	4	3	60,000	4	Delirium tremens; peripheral vascular collapse.
22	51	1	5	+	Lul	4	1	25,000	1	Peripheral vascular collapse; congestive failure.
23	49	7	7	+	Ruml	4	2	40,000	2½	Empyema; peripheral vascular collapse; congestive failure.
27	61	5†	4	+	Ruml	3	130	410,000	106	Thrombophlebitis (10th day); patient died in shock after femoral ligation; lung abscesses (autopsy).
29	76	4	21	+	Lul	4	1	25,000	½	Arteriosclerotic heart disease with failure; peripheral vascular collapse.
43	56	7	6	+	Ll, Rul	4	‡	300,000	48	Chronic nephritis; anuria (after sulfonamides); patient died in uremia 14 days after penicillin started; lungs clear for 6 days before death.
44	43	3	4	+	Rml	4	2	25,000	2	Chronic alcoholism; bronchiectasis; severe peripheral vascular collapse.
51	54	4	? 4	—	B	4	18	255,000	46	Chronic alcoholism; cirrhosis of liver; ascites; congestive failure; Type 4 pneumococcus in ascitic fluid.

\*R = right; L = left; u = upper; m = middle; l = lower; B = bilateral bronchopneumonia.

†Also had Type B Friedländer's bacillus in sputum and in lung abscesses (autopsy).

‡Continuous intravenous infusion.

improvement in the acute symptoms of the pneumonia.

Active delirium tremens developed in four cases; in each case during the second day of penicillin treatment. In one of the cases of Group I it lasted for four days, and in another it lasted for seven days. In the latter, improvement did not occur until after penicillin was stopped and a sulfonamide was given (Case 33). In one of the Group II cases the active delirium continued for two days; in the other it lasted for three days.

One patient developed hemolytic *Staphylococcus aureus* tonsillitis eight days after penicillin treatment was stopped. Another patient, who had first been treated with sulfonamides, developed an exacerbation of a chronic pyelonephritis with a positive blood culture<sup>2</sup> for hemolytic *Staph. aureus* on the fourteenth hospital day, five days after penicillin treatment was stopped. He recovered after a second

tions that could be attributed to the penicillin. In one case, a left-sided sciatic neuritis developed one week after penicillin treatment was completed. This may possibly have resulted from local nerve injury or from fibrosis about the nerve at the site of penicillin injections. In a second case, a morbilliform rash appeared about the knees, elbows and ankles after 475,000 units of penicillin had been given. The rash persisted for thirty-six hours after all therapy other than penicillin was discontinued, but it could not subsequently be reproduced with a total of 90,000 units given over twelve hours.

### *Fatal Cases*

Some of the significant findings in the 10 fatal cases are listed in Table 5. For the most part these cases were of extreme severity in patients who were either old or had severe underlying diseases. Almost all of them had multiple-lobe involvement and

bacteremia, and treatment was started late in the disease.

Two of the patients died several days after their pulmonary lesions had apparently cleared. One of them (Case 27) had been treated with penicillin alone and died suddenly after ligation of the femoral

These 7 patients were all essentially moribund when penicillin treatment was started.

### Penicillin Sensitivity of the *Pneumococcus* Strains

Tests for sensitivity to penicillin were carried out on thirty-six strains of pneumococci isolated from

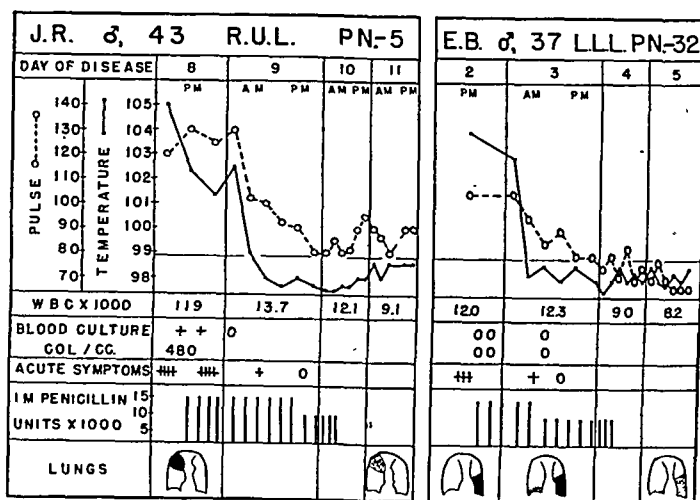


FIGURE 2. Course and Treatment in Case 8 (left) and Case 15 (right). These charts illustrate the rapid response to penicillin in cases of moderate severity.

vein for thrombophlebitis. Multiple abscesses were found in the lungs at autopsy, and cultures yielded a Friedländer's bacillus. The other patient (Case 43) died of sulfadiazine anuria and uremia after two days of penicillin treatment. A third patient (Case 51) had cirrhosis of the liver, congestive cardiac

as many cases. The results are summarized in Table 6. The minimum inhibiting concentration was 0.016 units or less per cubic centimeter for twenty-seven of the strains, and 0.032 units for the remaining nine strains. In several cases pneumococci of the same type isolated from the blood and sputum of the same patient were tested simultaneously and identical results were obtained with each. Blood levels corresponding to the minimum inhibiting

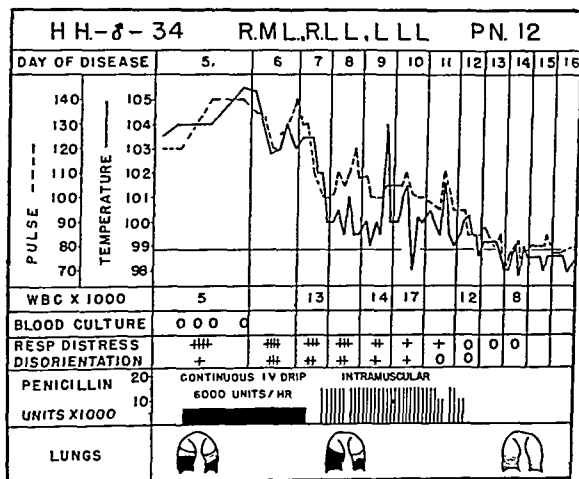


FIGURE 3. Course and Treatment in Case 12.

The chart shows the delayed clinical response to penicillin in a patient who was severely ill but had negative blood cultures.

failure and a Type 4 pneumococcus peritonitis (infected ascites) and died after two days on penicillin. Of the 7 remaining patients, 6 died within four hours of the first dose and one died eight hours after it.

TABLE 6. Penicillin Sensitivity of *Pneumococcus* Strains.

MINIMUM INHIBITING CONCENTRATION units/cc.	NO. OF STRAINS		ALL CASES
	GROUP I CASES	GROUP II CASES	
0.004	1	—	1
0.008	3	1	4
0.016	18	4	22
0.032	6	3	9
Totals	28	8	36

concentrations or higher were rarely maintained for more than two hours after an intramuscular injection of 15,000 units. There seemed to be no correlation, however, between the sensitivity of the strains and the clinical response.

### COMMENT

The results obtained in this series of extremely severe cases of pneumococcal pneumonia indicate that penicillin is a highly effective therapeutic agent in this disease. The results in the Group II cases show, in addition, that penicillin is equally effective in cases that are relatively resistant to

sulfonamide drugs as judged from the clinical and bacteriologic response. Among the 17 cases of this group, 10 had positive blood cultures after treat-

cases had the same mortality. Among the 46 cases reported by Tillett, Cambier and McCormack<sup>14</sup> there were only 5 deaths (6 per cent). The difference is readily accounted for by the much greater severity of the present cases. Many patients were essentially moribund when treatment was started; seven of them died a half to eight hours after the first dose, and the others had severe complications.

The clinical response to penicillin in the patients who recovered was quite similar to that which occurs under sulfonamide therapy. Fever and acute symptoms subside rapidly, usually within twenty-four to forty-eight hours. In general, the severe cases in which there is bacteremia and multiple-lobe involvement and those with various complications respond more slowly than do the milder and uncomplicated cases. Improvement in the general condition as well as in the subjective symptoms

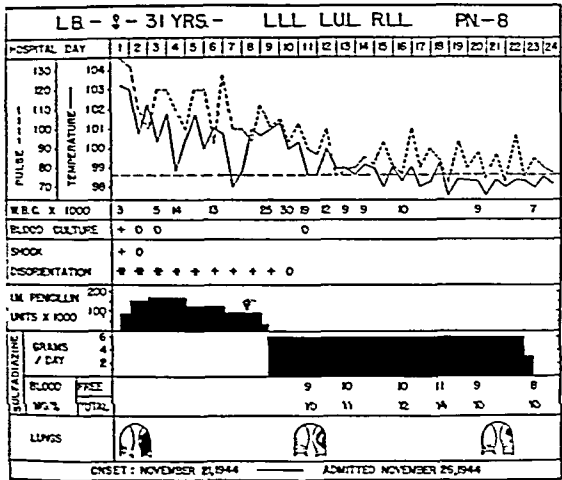


FIGURE 4. Course and Treatment in Case 33. The patient had active delirium tremens and persistent fever and respiratory symptoms during almost eight days of penicillin therapy. She improved rapidly after the penicillin was discontinued and a sulfonamide given. The physical and x-ray findings suggested the presence of interlobar pleural fluid and possibly cavitation in the lung, but the lungs cleared completely without special treatment.

ment with sulfonamides for varying periods up to six days. Only 3 of these patients died after penicillin therapy, one within four hours and the other

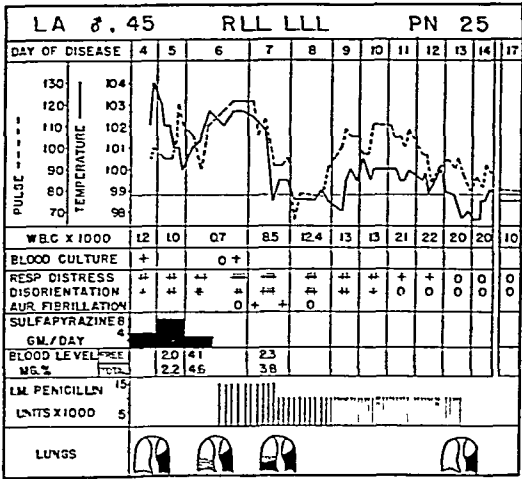


FIGURE 6. Course and Treatment in Case 39. There was a recurrence of bacteremia, together with persistence of a marked leukopenia and extension of the pneumonia, after two days of sulfonamide therapy. A slow but steady improvement occurred under treatment with penicillin.

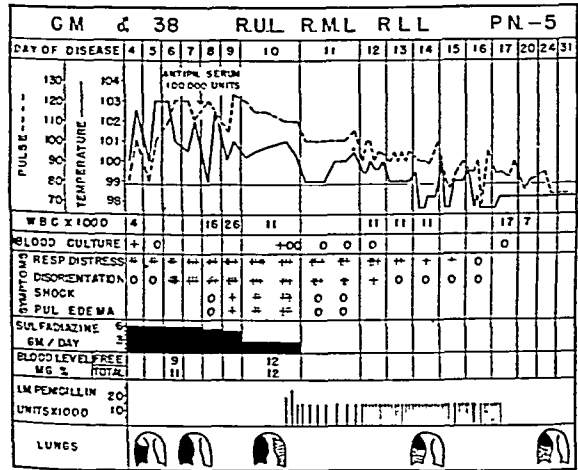


FIGURE 5. Course and Treatment in Case 38. In this patient the symptoms persisted, the pneumonia extended and bacteremia recurred after six days of treatment with sulfadiazine and three days after specific antiserum was given. The bacteremia cleared rapidly but symptomatic improvement occurred slowly after penicillin was given.

within two from causes other than the pulmonary infection. There were 10 deaths in this series, a mortality of 19 per cent. Both the Group I and the Group II

often preceded the drop in temperature, as is the case with sulfonamide therapy. The definite impression was gained that in the extremely severe cases this objective and symptomatic improvement was prompter with penicillin than in similar cases treated with sulfonamides. This may be related to the lag phase in the action of sulfonamides, which probably occurs in patients as well as in the test tube. Delays in the clinical response under penicillin therapy have usually been associated with other underlying diseases, with mixed infections or with purulent or other complications. In severe but otherwise uncomplicated cases a delay in response may result from inadequate dosage. Penicillin obviously has a distinct advantage over sulfonamides in patients with cardiac, renal or hepatic disease, in whom there is often difficulty in maintaining a proper fluid balance. With peni-

cillin it is not necessary to give alkalis and large amounts of fluids, which may result in serious water retention in such cases. Moreover, there is some evidence that in patients having a relatively low urinary output, and particularly in those with azotemia, higher penicillin levels are more readily maintained than in those with normal cardiorenal function having a large fluid output.

The failure of purulent complications to develop after penicillin treatment was begun is of interest in view of the severity of these cases and the high incidence of bacteremia. This is probably related to the effect that penicillin has in reducing the invasiveness of the susceptible organisms, as indicated by the prompt clearing of the bacteremia

were not ex of the cases intramuscul four to fort mild cases probably r every two twenty-four smaller am three days. must be ju response to treatment e side is sugg both in thi now being during pen eliminated from the b mococci m after clinic

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lished effectiveness of both agents and the temporary limitation of supply of penicillin, the indications for penicillin may be stated tentatively as follows.

Penicillin is the treatment of choice and should be used from the start in the following cases: in patients who are extremely ill and in a shocklike state; in patients with severe cardiac, renal or hepatic damage, particularly if there is edema or azotemia; if there is severe leukopenia; and in patients who are known to be sensitive to sulfonamides and have rashes, fever or severe nausea and vomiting early in the course of treatment with these drugs.

A change to penicillin from sulfonamides is indicated in patients who have received adequate doses and attained adequate blood levels but have failed to respond with improvement in the symptoms and a significant drop in temperature and pulse rate after twenty-four hours or longer, particularly if there is spread of the pulmonary lesion, persistent bacteremia or an increase in the number of pneumococci in the sputum as seen in direct smears; this change is also indicated if leukopenia, delirium tremens, auricular fibrillation or pulmonary edema develops before the symptoms of pneumonia have cleared or if severe untoward reactions, such as acute hemolytic anemia, gross hematuria, oliguria, anuria, nitrogen retention and even drug rash, occur before the pulmonary infection has been controlled. Crystalluria or microscopic hematuria need not be considered a cause for stopping sulfonamides but is an indication for alkalis and for increasing the fluid intake. Penicillin may be used locally when infected pleural fluid or other accessible foci of infection develop, and oral sulfonamides may be continued in such cases.

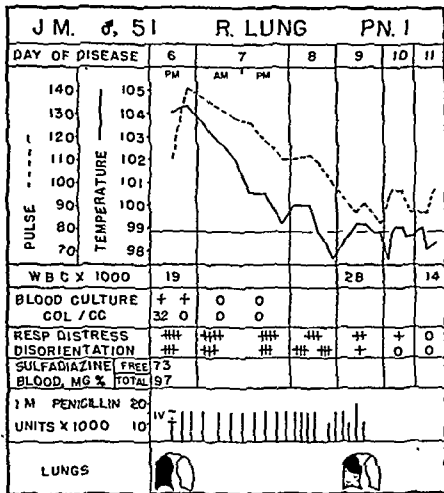


FIGURE 7. Course and Treatment in Case 40.

This patient had a severe pneumonia with involvement of the entire right lung on admission. He had been treated with sulfadiazine at home for about six days and had an adequate blood level of the drug on entry to the hospital. There was a steady drop in temperature after penicillin treatment was started, and clinical improvement followed.

after penicillin was started. On the other hand, the failure of some established purulent complications to clear following parenteral penicillin therapy is probably due to the failure of the agent to penetrate the infected foci in adequate amounts. It is possible, however, that early and more intensive treatment might result in the clearing of some of these focal infections before they become well established, as is often the case with sulfonamide therapy. Local instillation of penicillin into purulent foci may bring about additional cures. It should be emphasized that early diagnosis and treatment are still extremely essential if success is to be attained in saving life and in preventing serious complications.

It is not possible, on the basis of the available data, to define the effective dosage of penicillin for cases of pneumonia. The amounts used in the present cases were considerably greater than those employed by Tillett. These results suggest that the larger amounts were probably necessary and

## SUMMARY AND CONCLUSIONS

Penicillin was used in the treatment of 54 severe cases of typed pneumococcal pneumonia. Sulfonamides had previously failed to control the infection in 17 of these cases.

Bacteremia cleared rapidly, usually after the first dose of penicillin. Fever and acute symptoms subsided in most cases within twenty-four to forty-eight hours. Subjective improvement often preceded the drop in temperature.

There were 10 deaths. Seven of these were in moribund patients and occurred within a few hours after treatment was begun; the other 3 were associated with severe complicating conditions.

Purulent complications did not develop in any of these cases following penicillin therapy.

Penicillin was equally effective in the patients in whom it was used alone and in those who had previously failed to respond to sulfonamides.

Tentative indications for penicillin are given, and the dosage is discussed.

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## LISTERELLOSIS

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**L**ISTERELLOSIS is a sporadic, infectious disease occurring naturally in man<sup>1-22</sup> and in animals,<sup>23</sup> including cattle, sheep, goats, swine, foxes, chickens, rabbits, guinea pigs, gerbils and rats.<sup>24</sup> The disease is caused by *Listerella monocytogenes* (Bergey) and is characterized by symptoms principally referable to the central nervous system.

The causative organism, *List. monocytogenes*, was first submitted as a new species (*Bacterium monocytogenes*) in 1924 by Murray, Webb and Swann,<sup>25</sup> who isolated it from an epizootic affecting their laboratory rabbits and guinea pigs. In 1929, Nyfeldt<sup>21</sup> recovered the organism from the blood stream of a seventeen-year-old boy<sup>6</sup> with infectious mononucleosis, thereby being the first observer to prove definitely that *List. monocytogenes* is harbored by human beings. In 1918, Dumont and Cotoni<sup>2</sup> studied a diphtheroid organism isolated from the cerebrospinal fluid of a twenty-four-year-old soldier, which Paterson<sup>26</sup> over twenty years later identified as *List. monocytogenes*. It is highly probable that the diphtheroid organisms isolated from cases of meningitis in 1915 by Atkinson<sup>1</sup> and in 1919 by Dick<sup>3</sup> were *Listerella*.

## Epidemiology

Far too few cases are available for study to yield any clear-cut epidemiologic pattern of human listerellosis. Sufficient information is known, however, to avoid some blind pathways of exploration in an attempt to construct an epidemiologic fabric.

Including the probable cases,<sup>1, 3-5, 10</sup> — that is those in which the isolated organisms were described as diphtheroids but appear to have been *Listerella*, — listerellosis in human beings has been reported in Australia, France, Denmark, Scotland, Norway, Uruguay, Argentina, England and the United States (Illinois, Iowa, New York, Connecticut, Massachusetts, North Carolina, Missouri and California) (Table 1). Areas other than those cited for human infection in which spontaneous listerellosis has been recognized in animals include Sweden, South Africa, New Zealand, Germany and Russia, as well as Indiana, New Jersey, Colorado, Oregon, Minnesota, Arkansas, Vermont and Virginia.<sup>23</sup> Thus, it is quite evident that *List. monocytogenes* is well dispersed throughout the world.

A noteworthy fact is that Paterson's study of fifty-four strains of *Listerella*<sup>26</sup> revealed no relation between the bacteriologic type and the zoologic host species (man and animals), nor did the types

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TABLE 1. Data of 36 Human Cases of *Listerellosis*.

AUTHOR	DATE OF OCCURRENCE	STATE OR COUNTRY	AGE	SEX	CLINICAL DIAGNOSIS	BLOOD CULTURE	SPINAL-FLUID CULTURE	OUTCOME
Atkinson <sup>1</sup>	1915	Australia	2 yr. 4 yr. 3½ yr. 9 yr. 2 yr. 24 yr.	M M F F M M	Meningitis Meningitis Meningitis Meningitis Meningitis Meningitis	Not done Not done Not done Not done Not done Negative	Diphtheroid Diphtheroid Diphtheroid Diphtheroid Diphtheroid Diphtheroid (identified as <i>Listeria</i> by Paterson <sup>26</sup> )	Death Death Death Death Recovery Death
Dumont and Cotoni <sup>2</sup>	1918	France						
Dick <sup>3</sup>	1919	Illinois	49 yr.	M	Meningitis	Diphtheroid	Diphtheroid	Death
Baldrige et al. <sup>4*</sup>	About 1925	Iowa	Not given Not given Not given Not given Not given	Not given Not given Not given Not given Not given	Infectious mononucleosis Infectious mononucleosis Infectious mononucleosis Infectious mononucleosis Infectious mononucleosis	Diphtheroid Diphtheroid Diphtheroid Diphtheroid Diphtheroid	Not done (diphtheroid isolated from lymph-node biopsies)	Recovery Recovery Recovery Recovery Recovery
Kessel and Romanoffs	1929	New York	39 yr.	M	Meningitis	Diphtheroid	Diphtheroid	Recovery
Nyfeldt <sup>5</sup>	1929 and 1930	Denmark	17 yr. 33 yr. 19 yr.	M M F	Infectious mononucleosis Infectious mononucleosis Infectious mononucleosis	Listerella Listerella Listerella	Not done Not done Not done	Recovery Recovery Recovery
Burn <sup>7</sup>	1933 and 1934	Connecticut	1 day Premature infant 8 days 53 yr.	M F F M	Meningitis Meningitis Meningitis Meningitis	Listerella Listerella Listerella Listerella	Not done Not done Not done Not done	Death Death Death Death
Schultz et al. <sup>8</sup>	1933	California	Adult	F	Meningitis	Not done	Listerella (Type 3 pneumococcus isolated from brain)	Recovery
Gibson <sup>9</sup>	1934	Scotland	37 yr.	M	Meningitis	Not done	Diphtheroid (identified as <i>Listeria</i> by Webb and Barber <sup>22</sup> )	Death
Tesdall <sup>10</sup>	1934	Norway	31 yr.	F	Meningitis	Negative	Diphtheroid (identified as <i>Listeria</i> by Webb and Barber <sup>22</sup> )	Death
Burn <sup>11</sup>	1935	Connecticut	26 yr.	M	Meningitis	Not done	Not done ( <i>Listeria</i> recovered from brain)	Death
Carey <sup>12</sup>	1935	Massachusetts	3¼ yr.	M	Meningitis	Not done	Listerella	Recovery
Poston et al. <sup>13</sup>	1936	North Carolina	3 yr.	M	Meningitis	Not done	Not done ( <i>Listeria</i> recovered from brain)	Death
Porzecanski and De Baygorria <sup>14</sup>	1937	Uruguay	19 yr	M	Meningitis	Not done	Listerella	Recovery (patient treated with Prontosil 27)
Schmidt and Nyfeldt <sup>15</sup>	1937	Denmark	16 yr. 18 yr. 24 yr. 14 yr.	F F M M	Infectious mononucleosis Infectious mononucleosis Infectious mononucleosis Infectious mononucleosis	Negative Negative Listerella Listerella	Listerella Listerella Listerella Listerella	Recovery Recovery Recovery Recovery
Wright and MacGregor <sup>16</sup>	1938	Scotland	1½ yr.	M	Meningitis	Not done	Not done ( <i>Listeria</i> isolated, but source not given)	Recovery (patient treated with sulfanilamide)
Porter and Hale <sup>17</sup>	1939	Iowa	Child	M	Meningitis	Not done	Not done ( <i>Listeria</i> isolated, but source not given)	Recovery (patient treated with sulfanilamide)
Pons and Julianelle <sup>18</sup>	1939	Missouri	16 yr.	F	Infectious mononucleosis	Listerella	Not done	Recovery (patient treated with sulfapyridine)
Savino <sup>19</sup>	1939	Argentina	67 yr.	F	Meningitis	Negative	Listerella	Recovery (patient treated with sulfapyridine)
Webb <sup>20</sup>	1943(?)	England	20 yr.	M	Infectious mononucleosis	Listerella	Not done	Recovery

\*In Baldrige's cases the diagnosis of listerellosis is doubtful.

appear to be associated with a particular geographic origin.

To date, the number of human cases from which *List. monocytogenes* has been isolated and identified is 23. Adding the probable cases, the total becomes 36. Of these 36 cases, 15 (42 per cent) terminated fatally. Computing the fatality after subtracting 14 cases diagnosed as infectious mononucleosis (for reasons given below), the mortality of human listerellosis in its typical meningeal form approximates 68 per cent. This latter figure would be higher (79 per cent) if the recent cases treated with sulfonamides were excluded.

The natural habitat of the organism is not known. The part played by animals as a reservoir of infection for human beings is questionable. Their role appears to be unimportant, but any opinion on this score should be given reservedly until there accrue more data on human infection. It is noteworthy, however, that in areas in which listerellosis is enzootic (the United States, — Illinois, New York and Iowa, — England, Germany and New Zealand), very few cases of human infection have been reported. Indeed, in only a single case of human infection has there been recorded the remotest possibility of exposure (to a pet rabbit ill with so-called "snuffles" that was not further examined<sup>7</sup>).

Other than probable transplacental infection occurring in the newborn,<sup>7</sup> the portal of entry of the organism in human beings is obscure. Julianelle<sup>27</sup> thinks that ingestion and penetration through the gastrointestinal tract are likely because of the successful infection of white mice by means of contaminated drinking water, whereas inoculation of a culture intranasally into highly susceptible rabbits failed to cause infection. In domestic animals, experimental production of listerellosis to simulate a spontaneous infection is difficult regardless of the method of infection utilized. The nasal route appears to be the likeliest pathway in natural infection of animals<sup>28, 29</sup> but further work is needed to resolve this question.

Except for a convalescent carrier,<sup>8</sup> the isolation of *List. monocytogenes* has been accomplished only in actively diseased animals and man. The few attempts to discover healthy carriers in man have met with failure.<sup>7</sup> These few negative findings by no means eliminate the possibility of latent, indiscernible infection that flares into active disease under propitious conditions. The latter explanation, for example, can be applied to those cases of infection of the newborn that have occurred in human beings,<sup>7</sup> cows<sup>30, 31</sup> and sheep,<sup>32</sup> in which the parent was apparently unaffected by the organism. Predisposing causes that are capable of producing a general lowering of resistance have been reported in several human cases,<sup>1, 3, 5, 7, 13, 16</sup> and these are believed to exert an appreciable influence in producing the disease in animals.

All age groups and both sexes have been affected with listerellosis. The occurrence of the disease in the newborn,<sup>7</sup> one of these patients being a three-week premature infant, is particularly interesting because of the incrimination of *Listerella* as a cause of abortion in cattle<sup>30-33</sup> and sheep.<sup>32</sup>

The isolation of *List. monocytogenes* from the blood or cerebrospinal fluid in 9 cases of infectious mononucleosis (Table 1) merits separate consideration. Three other isolated strains mentioned by Paterson<sup>26</sup> are not considered in this paper because of insufficient data. Murray, Webb and Swann<sup>25</sup> first noted the typical mononuclear response in the blood of rabbits affected with listerellosis. It was to be expected, therefore, that the blood picture seen in human beings with infectious mononucleosis would be ascribed to the same cause.<sup>6, 15</sup> The available evidence, however, controverts this assumption. A filterable virus associated with infectious mononucleosis has been shown by van den Berghe, Liessens and Kovacs<sup>34, 35</sup> and Nettleship.<sup>35</sup> Julianelle, Bierbaum and Moore<sup>37</sup> were unable to confirm these findings. Paterson<sup>26</sup> studied the antigenic structure of fifty-four strains of *Listerella* isolated from a variety of animals and from human beings. Ten of these strains were isolated from patients with infectious mononucleosis, and they comprised a distinct group (Group 3) in his classification of four groups. Serologic evidence against an etiologic relation between *Listerella* and infectious mononucleosis has been demonstrated by Kolmer,<sup>38</sup> Julianelle<sup>27</sup> and Janeway and Dammin.<sup>39</sup> Furthermore, the benignity of the cases of infectious mononucleosis from which *List. monocytogenes* was isolated, in contrast to the high mortality that occurred in the typical meningeal form of listerellosis, supports the likelihood that the organism was acting in the capacity of an adventitious invader. The possibility of a mutual relation between the discovered filterable virus and *List. monocytogenes* in the pathogenesis of infectious mononucleosis should be kept in mind. In this respect, the well-known virus-bacteria combination in the production of swine influenza may be pointed out as an established fact.

The sporadicity of human listerellosis indicates a low degree of communicability. A study of the case histories, however, reveals some possibly significant facts. Burn<sup>7</sup> reported 2 infants born the same day in the visiting obstetric service of a hospital. The infant delivered early in the morning died the next day of listerellosis. The second infant, apparently delivered later on the same day, suddenly became ill eight days later and died of listerellosis within six days. Atkinson's<sup>4</sup> 5 cases in children all occurred within a period of thirteen days. Until further information is available concerning interhuman communicability of listerellosis, it is unwise to ascribe the cited cases to pure coincidence.



Thus, the usual communicable-disease precautions should be applied to listerellosis. There is little question of the communicability of the disease in animals.

### Symptoms and Signs

Because of the protean symptomatology of infectious mononucleosis and the likelihood that a *Listerella* is merely a fortuitous invader in the disease, only the meningeal form of listerellosis will be considered.

The usual clinical picture seen in all ages is that of a septicemia with severe meningoencephalitic involvement. In children and adults the following observations have been made: sudden or gradual illness with fever, vomiting, headache, lethargy, stupor, irrationality, loss of reflexes, convulsions, rigidity of the neck, strabismus, ptosis, diplopia and bilateral mastoiditis. In fatal cases, death usually occurred within a week. Many patients who recovered had a prolonged convalescent period. In 1 case, affecting a nurse,<sup>8, 22</sup> ten weeks after the inception of symptoms a speech defect, impaired memory, emotional instability, difficulty in self-feeding, slight nodding of the head and a sprawling gait were present. *List. monocytogenes* was recoverable in the cerebrospinal fluid for over four months. In the newborn, signs were apparent at birth or two to eight days later.<sup>7</sup> Refusal of food, diarrhea, cyanosis, drowsiness and clonic convulsions were noted. The 3 cases reported ended fatally within six days.

### Laboratory Findings

The cerebrospinal fluid has shown the most consistent changes. Increased pressure, a positive Pandy reaction, an increased number of leukocytes (predominantly lymphocytes), intracellular and extracellular *Listerella* organisms in stained smears and recovery of the organism in pure culture have been recorded.<sup>1-3, 5, 8, 10, 12, 13, 16, 18, 19</sup>

A moderate leukocytosis has been the one common hematologic observation in the few blood examinations performed. The interpretation of the differential count has been confused because of changes attributable to infectious mononucleosis when the latter disease has accompanied the isolation of *List. monocytogenes* from the blood. In cases in which listerellosis alone was present, neutrocytosis was originally found.<sup>7, 9, 12-14, 19</sup>

### Post-Mortem Findings

The post-mortem findings included suppurative leptomeningitis and ependymitis, purulent otitis media, focal necrosis and patchy fatty degeneration of the liver, a swollen and congested spleen, focal necrosis of the adrenal glands, atelectasis, focal pneumonia and bronchiolitis.<sup>1, 7, 9, 13</sup>

### Treatment

Before the advent of the sulfonamides, symptomatic treatment had been relied on with little success. Three patients with the meningeal form of listerellosis were treated with sulfanilamide,<sup>17</sup> sulfapyridine<sup>19</sup> and Prontosil, respectively.<sup>40</sup> Recovery ensued in all 3 cases.

Experimentally, Webb<sup>20</sup> achieved favorable results with sulfanilamide and sulfapyridine in mouse listerellosis. His best results were obtained with a therapeutic combination of sulfapyridine and specific antilisterella rabbit serum. Savino<sup>41</sup> infected white rats with *List. monocytogenes* and noted a protective action with sulfapyridine. Porter and Hale<sup>17</sup> reported that both sulfanilamide and sulfapyridine were therapeutically effective in mice experimentally infected with listerellosis. In-vitro tests showed penicillin to be ineffective against *List. monocytogenes*.<sup>42</sup>

### SUMMARY

There have been reported in the literature 23 definitely diagnosed and 13 probable cases of human listerellosis. In its typical meningeal form, this disease showed a mortality of approximately 79 per cent, excluding 3 cases treated with sulfonamides.

Ecologic, age and sex factors appear to be of little significance in the incidence of this disease.

The natural habitat and portal of entry of *Listerella monocytogenes* — other than transplacental infection in the newborn — are unknown. The nasal and gastrointestinal tracts appear as the likeliest routes of penetration.

The status of a healthy or latent carrier of *List. monocytogenes* has not been proved in man or animals. The facts that infection of the newborn can occur with no effect on the parent, that a *Listerella* bacteremia may be present in cases of infectious mononucleosis and that certain predisposing factors apparently produce active infection, however, suggest that latent carriers play a significant role in the pathogenesis of listerellosis.

At present there is little evidence to incriminate animals as direct transmitting agents of *List. monocytogenes* to human beings. The widespread prevalence of listerellosis in animals, however, establishes them as possible reservoirs of infection for man.

The significance of *List. monocytogenes* in cases of infectious mononucleosis is discussed. It is believed that the organism acts as a contingent invader in infectious mononucleosis rather than as an incitant of the disease. The possibility of a mutual virus-bacteria relation in infectious mononucleosis is pointed out.

Circumstantial evidence is cited supporting the possibility of interhuman communicability in active cases of listerellosis, thus making advisable the practice of communicable-disease precautions whenever this disease is encountered.

Clinically and at autopsy, listerellosis is characterized by a meningoencephalitic syndrome. The most usual spinal-fluid changes were increased pressure, globulin and leukocytes. A moderate neutrocytosis occurred early in the disease.

Treatment with Prontosil, sulfanilamide and sulfapyridine appears to have been successful.

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## MEDICAL PROGRESS

### SKIN TESTS IN BACTERIAL AND VIRAL DISEASES\* (Concluded)

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#### SKIN TESTS EMPLOYING BACTERIAL TOXINS

##### *Schick Test*

In 1908, Schick<sup>85</sup> showed that the toxin of the diphtheria bacillus is capable of eliciting dermal reactions in certain persons. His subsequent publications<sup>86, 87</sup> announced that this test could be used as an index of immunity or susceptibility to diphtheria. His experiments indicated that a negative intracutaneous reaction usually means a high enough level of antitoxin to protect against the disease. The test dose of toxin was originally defined by Schick on an empirical basis as 1/50 of a guinea-pig M. L. D. (minimal lethal dose). This level was selected by him because he thought that persons who failed to react to this dose possessed sufficient antitoxin to protect them against all but the so-called "septic type" of diphtheria. In subsequent years when cases of diphtheria were reported in Schick-negative reactors there was some question whether the Schick test dose of 1/50 M. L. D. should not be increased. This problem was considered in 1931 by the Biological Standardization Commission of the League of Nations, and the 1/50 M. L. D. recommended by Schick was adopted by the commission as representing the optimal test dose. It was further recommended that Schick toxin be standardized by determining its combining power as well as its toxicity. The reason for this recommendation is that filtrates of diphtheria cultures contain varying quantities of substances that although unable to elicit the dermal reaction can combine with antitoxin. Hence, toxin standardized by means of toxicity alone varies in its ability to elicit dermal reactions, depending on the extent to which antibody has been eliminated locally by these nontoxic substances. The validity of these recommendations has been questioned by Taylor and Moloney,<sup>88</sup> who were unable to find that the combining power of Schick toxin had any significance for human beings with respect to the level of antitoxin detected. Furthermore, they recommended a dose of toxin containing three times the level usually employed (1/50 M. L. D.). Thus the question of the proper toxin level to be used in the Schick test is still an open one.

In 1913, Schick<sup>86</sup> noted that occasionally false-positive dermal reactions may occur. These reactions appeared a little earlier than the true re-

actions, reached their maximum intensity sooner and faded more quickly. Bessau and Schwenke<sup>89</sup> found that, when the toxin is destroyed by heat, false-positive reactions still occur. As a result of this observation, a control injection of heated toxin was introduced into the Schick test. It soon became apparent that this so-called "pseudoreaction" was due to hypersensitivity to the protein of the diphtheria bacillus. The reaction is highly specific and indicates some previous contact with the diphtheria bacillus. It is usually absent in infants and becomes more frequent as age advances. Further experience with the Schick control showed that immunizing injections often gave rise to unpleasant reactions in those exhibiting pseudoreactions. Thus the control not only came to serve as an indicator of false-positive reactions, but also indicated those subjects who might react severely to immunizing injections.

Moloney and Fraser<sup>90</sup> have advised employing a 1/20 dilution of diphtheria toxoid as a substitute for the heated-toxin control in the Schick test. They believe that this material is a better control, as well as an efficient indicator of those persons who will give severe reactions when immunized with toxoid. These reactions usually consist of chills, fever, general malaise, nausea and vomiting. This test has been frequently referred to as the Moloney test. Although it is of unquestioned value in determining when subjects are hypersensitive to bacterial protein, — and hence should be immunized cautiously with toxoid, — it is not a true control because the toxoid may contain one hundred times as much bacterial protein as does the Schick toxin. As a consequence of the higher bacterial protein content more persons react to the Moloney control than to the Schick control, thus making the Schick test more difficult to interpret.

The Moloney test, however, should be done on all Schick-positive subjects over the age of five who are to be immunized with toxoid.<sup>91</sup> The 1:20 dilution of toxoid originally proposed by Moloney and Fraser was found to be too strong, and as a result a dilution of 1/100 is most generally used at present. The test is performed by injecting 0.1 cc. of a 1:100 dilution of toxoid into the volar surface of the forearm. Readings are made in twenty-four and forty-eight hours. Significant reactions consist of an area of erythema greater than 1 cm. in diameter. Bunch and his co-workers<sup>92</sup> have recommended a scheme of immunization that is dependent on the degree of sensitivity to bacterial protein as demonstrated by the Moloney test.

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The Schick test is performed by injecting 0.1 cc. of Schick toxin intradermally in the volar surface of the right forearm. This is controlled by injecting the same volume of heated toxin in the same manner in the left arm. Readings should be made at the end of two and of four days and are interpreted as follows:

*Positive reaction.* An area of erythema and infiltration measuring at least 10 mm. in diameter appears in twenty-four to thirty-six hours on the right arm and reaches its greatest intensity in four or five days. There should be no reaction on the left (control) arm. This response indicates susceptibility to diphtheria.

*Positive-combined reaction.* Reactions measuring at least 10 mm. are present on both arms in two days. The control reaction, however, fades by the fourth day, the time when the true reaction reaches its height. This response indicates susceptibility to diphtheria and sensitivity to diphtheria-bacillus protein.

*Pseudoreaction.* Reactions occur on both arms and run a similar course, reaching a peak on the second or third day and fading by the fourth. Persons showing this response are hypersensitive to diphtheria-bacillus protein but presumably immune to diphtheria.

*Negative reaction.* No reaction occurs, or one less than 10 mm. in one or both arms. This indicates that the subject has little or no sensitivity to diphtheria-bacillus protein and is probably immune to diphtheria.

A few reports have appeared in the literature describing cases of acute anaphylactic shock following the application of the Schick test. In 1936, Parish<sup>93</sup> described 14 cases of this character. Two of these patients were known to be sensitive to Witte peptone, an agent added to the toxin in order to stabilize it.

Following the acceptance of the Schick test dose as 1/50 M. L. D., a large number of experiments have indicated that this amount of toxin does not produce a dermal reaction on intracutaneous injection into human beings if the blood serum contains more than 1/30 unit of antitoxin per cubic centimeter. This value had for many years been generally regarded as representing the so-called "Schick level" of immunity. During the last few years, however, a number of reports have appeared indicating that this level is more accurately described by a considerably smaller amount of antitoxin. Glenny and Waddington<sup>94</sup> found that the Schick-negative level in guinea pigs corresponds to 1/250 unit of antitoxin per cubic centimeter of serum. Others<sup>95</sup> have shown that the level in man lies between 1/500 to 1/250 unit per cubic centimeter. Although Phair<sup>96</sup> accepts 1/100 unit of antitoxin as the threshold level, he found that 9.3 per cent cases of the Schick-positive group that he tested had sufficient antitoxin so that the test should have been negative. In addition, 7.5 per cent of the negative reactors had a level of antitoxin that should have rendered them positive. These conflicting results indicate that with the methods for measuring antitoxin now available, there is no precise Schick level of antitoxin that can be determined above which a person will be protected and below which he will be susceptible.

The failure to find a critical level of antitoxin as measured by the Schick test has cast some doubt as to its value as an index of susceptibility or immunity. Obviously only by long-continued observation of the behavior of groups of positive and negative Schick reactors can the value of this test be established. Although there are exceptions, the bulk of evidence that has accumulated since Schick's original publication in 1908 indicates that a negative Schick reaction means resistance against all *ordinary* risks of infection. This evidence is based on the following observations: there is almost no diphtheria in nurses who are Schick negative despite repeated exposures; there is an extremely low incidence of the disease in Schick-negative reactors in the population at large; virulent organisms can exist in the throats of Schick-negative reactors without producing the disease; and the results of challenge experiments add more evidence. Guthrie, Marshall and Moss<sup>97</sup> inoculated Schick-positive and Schick-negative persons with virulent diphtheria organisms and observed the disease in the former only. O'Brien, Okell and Parish<sup>98</sup> had occasion to observe an inadvertent experiment in which ten to twenty presumably lethal doses of toxin for man were injected intradermally into a known Schick-negative reactor; no symptoms occurred.

It must be kept in mind that immunity in diphtheria, as in any infectious disease, is only relative. Not only does the level of immunity fluctuate, but it may be broken down by massive infection. Despite this, the number of cases occurring in Schick-negative reactors is relatively few. O'Brien, Okell and Parish<sup>98</sup> followed 20,000 Schick-negative subjects for six years and were able to trace 18 cases of diphtheria, 17 of which were mild. Neale<sup>99</sup> reported 2 cases in Schick-negative persons, and Bauer<sup>100</sup> reported 21 cases occurring out of a total of 96,252 immunized and Schick-negative persons. Meersseman, Friess and Renard<sup>101</sup> noted a 1 per cent incidence of diphtheria in a Schick-negative group numbering several thousand. Robinson and Marshall<sup>102</sup> have observed 12 cases in which the Schick test was negative immediately prior to the onset of the disease. Underwood<sup>103</sup> reviewed the literature of diphtheria occurring in Schick-negative persons up to 1935 and reported 20 additional cases (1 per cent) occurring in 2761 known Schick negative reactors. In 19 of these cases the so-called "gravis" strain was isolated — an organism that is usually found in the severest cases. This suggests that the Schick test may not be an effective index of immunity against the gravis strain of organism. Many of the above reported cases were severe, showing that the disease is not always mild in Schick-negative cases. Parish and Okell<sup>104</sup> have shown that 1.1 per cent of 533 children who were originally Schick negative relapsed to a positive state within one to seven years, and 5 per cent of 440 vaccinated children relapsed during the same period. Since

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#### SKIN TESTS EMPLOYING BACTERIAL TOXINS

##### *Schick Test*

In 1908, Schick<sup>85</sup> showed that the toxin of the diphtheria bacillus is capable of eliciting dermal reactions in certain persons. His subsequent publications<sup>86, 87</sup> announced that this test could be used as an index of immunity or susceptibility to diphtheria. His experiments indicated that a negative intracutaneous reaction usually means a high enough level of antitoxin to protect against the disease. The test dose of toxin was originally defined by Schick on an empirical basis as 1/50 of a guinea-pig M. L. D. (minimal lethal dose). This level was selected by him because he thought that persons who failed to react to this dose possessed sufficient antitoxin to protect them against all but the so-called "septic type" of diphtheria. In subsequent years when cases of diphtheria were reported in Schick-negative reactors there was some question whether the Schick test dose of 1/50 M. L. D. should not be increased. This problem was considered in 1931 by the Biological Standardization Commission of the League of Nations, and the 1/50 M. L. D. recommended by Schick was adopted by the commission as representing the optimal test dose. It was further recommended that Schick toxin be standardized by determining its combining power as well as its toxicity. The reason for this recommendation is that filtrates of diphtheria cultures contain varying quantities of substances that although unable to elicit the dermal reaction can combine with antitoxin. Hence, toxin standardized by means of toxicity alone varies in its ability to elicit dermal reactions, depending on the extent to which antibody has been eliminated locally by these nontoxic substances. The validity of these recommendations has been questioned by Taylor and Moloney,<sup>88</sup> who were unable to find that the combining power of Schick toxin had any significance for human beings with respect to the level of antitoxin detected. Furthermore, they recommended a dose of toxin containing three times the level usually employed (1/50 M. L. D.). Thus the question of the proper toxin level to be used in the Schick test is still an open one.

In 1913, Schick<sup>86</sup> noted that occasionally false-positive dermal reactions may occur. These reactions appeared a little earlier than the true re-

actions, reached their maximum intensity sooner and faded more quickly. Bessau and Schwenke<sup>89</sup> found that, when the toxin is destroyed by heat, false-positive reactions still occur. As a result of this observation, a control injection of heated toxin was introduced into the Schick test. It soon became apparent that this so-called "pseudoreaction" was due to hypersensitivity to the protein of the diphtheria bacillus. The reaction is highly specific and indicates some previous contact with the diphtheria bacillus. It is usually absent in infants and becomes more frequent as age advances. Further experience with the Schick control showed that immunizing injections often gave rise to unpleasant reactions in those exhibiting pseudoreactions. Thus the control not only came to serve as an indicator of false-positive reactions, but also indicated those subjects who might react severely to immunizing injections.

Moloney and Fraser<sup>90</sup> have advised employing a 1/20 dilution of diphtheria toxoid as a substitute for the heated-toxin control in the Schick test. They believe that this material is a better control, as well as an efficient indicator of those persons who will give severe reactions when immunized with toxoid. These reactions usually consist of chills, fever, general malaise, nausea and vomiting. This test has been frequently referred to as the Moloney test. Although it is of unquestioned value in determining when subjects are hypersensitive to bacterial protein, — and hence should be immunized cautiously with toxoid, — it is not a true control because the toxoid may contain one hundred times as much bacterial protein as does the Schick toxin. As a consequence of the higher bacterial protein content more persons react to the Moloney control than to the Schick control, thus making the Schick test more difficult to interpret.

The Moloney test, however, should be done on all Schick-positive subjects over the age of five who are to be immunized with toxoid.<sup>91</sup> The 1:20 dilution of toxoid originally proposed by Moloney and Fraser was found to be too strong, and as a result a dilution of 1/100 is most generally used at present. The test is performed by injecting 0.1 cc. of a 1:100 dilution of toxoid into the volar surface of the forearm. Readings are made in twenty-four and forty-eight hours. Significant reactions consist of an area of erythema greater than 1 cm. in diameter. Bunch and his co-workers<sup>92</sup> have recommended a scheme of immunization that is dependent on the degree of sensitivity to bacterial protein as demonstrated by the Moloney test.

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The Schick test is performed by injecting 0.1 cc. of Schick toxin intradermally in the volar surface of the right forearm. This is controlled by injecting the same volume of heated toxin in the same manner in the left arm. Readings should be made at the end of two and of four days and are interpreted as follows:

*Positive reaction.* An area of erythema and infiltration measuring at least 10 mm. in diameter appears in twenty-four to thirty-six hours on the right arm and reaches its greatest intensity in four or five days. There should be no reaction on the left (control) arm. This response indicates susceptibility to diphtheria.

*Positive-combined reaction.* Reactions measuring at least 10 mm. are present on both arms in two days. The control reaction, however, fades by the fourth day, the time when the true reaction reaches its height. This response indicates susceptibility to diphtheria and sensitivity to diphtheria-bacillus protein.

*Pseudoreaction.* Reactions occur on both arms and run a similar course, reaching a peak on the second or third day and fading by the fourth. Persons showing this response are hypersensitive to diphtheria-bacillus protein but presumably immune to diphtheria.

*Negative reaction.* No reaction occurs, or one less than 10 mm. in one or both arms. This indicates that the subject has little or no sensitivity to diphtheria-bacillus protein and is probably immune to diphtheria.

A few reports have appeared in the literature describing cases of acute anaphylactic shock following the application of the Schick test. In 1936, Parish<sup>93</sup> described 14 cases of this character. Two of these patients were known to be sensitive to Witte peptone, an agent added to the toxin in order to stabilize it.

Following the acceptance of the Schick test dose as 1/50 M. L. D., a large number of experiments have indicated that this amount of toxin does not produce a dermal reaction on intracutaneous injection into human beings if the blood serum contains more than 1/30 unit of antitoxin per cubic centimeter. This value had for many years been generally regarded as representing the so-called "Schick level" of immunity. During the last few years, however, a number of reports have appeared indicating that this level is more accurately described by a considerably smaller amount of antitoxin. Glenny and Waddington<sup>94</sup> found that the Schick-negative level in guinea pigs corresponds to 1/250 unit of antitoxin per cubic centimeter of serum. Others<sup>95</sup> have shown that the level in man lies between 1/500 to 1/250 unit per cubic centimeter. Although Phair<sup>96</sup> accepts 1/100 unit of antitoxin as the threshold level, he found that 9.3 per cent cases of the Schick-positive group that he tested had sufficient antitoxin so that the test should have been negative. In addition, 7.5 per cent of the negative reactors had a level of antitoxin that should have rendered them positive. These conflicting results indicate that with the methods for measuring antitoxin now available, there is no precise Schick level of antitoxin that can be determined above which a person will be protected and below which he will be susceptible.

The failure to find a critical level of antitoxin as measured by the Schick test has cast some doubt as to its value as an index of susceptibility or immunity. Obviously only by long-continued observation of the behavior of groups of positive and negative Schick reactors can the value of this test be established. Although there are exceptions, the bulk of evidence that has accumulated since Schick's original publication in 1908 indicates that a negative Schick reaction means resistance against all ordinary risks of infection. This evidence is based on the following observations: there is almost no diphtheria in nurses who are Schick negative despite repeated exposures; there is an extremely low incidence of the disease in Schick-negative reactors in the population at large; virulent organisms can exist in the throats of Schick-negative reactors without producing the disease; and the results of challenge experiments add more evidence. Guthrie, Marshall and Moss<sup>97</sup> inoculated Schick-positive and Schick-negative persons with virulent diphtheria organisms and observed the disease in the former only. O'Brien, Okell and Parish<sup>98</sup> had occasion to observe an inadvertent experiment in which ten to twenty presumably lethal doses of toxin for man were injected intradermally into a known Schick-negative reactor; no symptoms occurred.

It must be kept in mind that immunity in diphtheria, as in any infectious disease, is only relative. Not only does the level of immunity fluctuate, but it may be broken down by massive infection. Despite this, the number of cases occurring in Schick-negative reactors is relatively few. O'Brien, Okell and Parish<sup>98</sup> followed 20,000 Schick-negative subjects for six years and were able to trace 18 cases of diphtheria, 17 of which were mild. Neale<sup>99</sup> reported 2 cases in Schick-negative persons, and Bauer<sup>100</sup> reported 21 cases occurring out of a total of 96,252 immunized and Schick-negative persons. Meersseman, Friess and Renard<sup>101</sup> noted a 1 per cent incidence of diphtheria in a Schick-negative group numbering several thousand. Robinson and Marshall<sup>102</sup> have observed 12 cases in which the Schick test was negative immediately prior to the onset of the disease. Underwood<sup>103</sup> reviewed the literature of diphtheria occurring in Schick-negative persons up to 1935 and reported 20 additional cases (1 per cent) occurring in 2761 known Schick negative reactors. In 19 of these cases the so-called "gravis" strain was isolated — an organism that is usually found in the severest cases. This suggests that the Schick test may not be an effective index of immunity against the gravis strain of organism. Many of the above reported cases were severe, showing that the disease is not always mild in Schick-negative cases. Parish and Okell<sup>104</sup> have shown that 1.1 per cent of 533 children who were originally Schick negative relapsed to a positive state within one to seven years, and 5 per cent of 440 vaccinated children relapsed during the same period. Since

several of the reported cases of diphtheria in Schick-negative reactors were not retested at close intervals, it is possible that the subjects had become Schick positive prior to the onset of the disease.

In summary, it may be stated that although there are reported failures, a negative Schick test usually means sufficient degree of immunity to protect against diphtheria. It is well known that there are persons who, having had an adequate primary stimulus but having lost with the lapse of time most of their demonstrable antitoxin, nevertheless react after exposure with the production of antitoxin rapidly enough to protect against the disease. This is seen in a number of persons who become Schick negative after the injection of the minute amount of toxin used in the Schick test. This of course is likeliest to occur in adults who have had repeated subclinical exposures. It is believed at present that a positive Schick test in adults does not necessarily mean susceptibility, whereas it is a much closer index of susceptibility in children.

### Dick Test

In 1924, the Dicks<sup>106</sup> injected 0.1 cc. of a 1:1000 solution of beta-hemolytic streptococcus toxic filtrate intradermally into a number of persons and found that those with no past history of scarlet fever gave an inflammatory response more frequently than did those with positive histories. They also found that this filtrate could be neutralized by convalescent scarlet-fever serum. On this basis they suggested that the skin test could be used as an index of immunity or susceptibility to scarlet fever.<sup>\*106</sup> They later reported 20,856 subjects who were Dick negative and went through repeated exposures to scarlet fever without contracting the disease.<sup>107</sup> Despite these rather impressive figures, not infrequent reports have appeared in the literature from time to time describing scarlet fever in Dick-negative reactors.<sup>108-111</sup> Since the Dick test measures only antitoxic immunity, a cause of the apparent failure of the Dick test may be that there is more than one antigenic strain of erythrogenic toxin.<sup>112-114</sup> Theoretically, infection with a streptococcus producing an erythrogenic toxin different from that used in the Dick test could produce a rash in Dick-negative reactors. Another possible source of false-negative reactions is the use of toxin of inferior potency because of the difficulty in standardizing the erythrogenic toxin. Despite the reported failures, it is generally believed that the Dick test is reliable enough to be used as an index of immunity to the rash of scarlet fever. There is no convincing evidence that Dick-negative reactors are less susceptible to streptococcal infections than Dick-positive ones.

Schwentker, Janney and Gordon<sup>110</sup> have recently reported their careful study of a scarlet-fever and

tonsillitis epidemic in Rumania that was caused by a Type 10 hemolytic streptococcus. They have clearly shown that although a negative Dick test usually indicates immunity to scarlet fever, a positive reaction does not necessarily mean susceptibility. Thus, in the group who became asymptomatic carriers of the type of streptococcus responsible for the then current scarlet-fever epidemic, there were equal numbers of Dick-positive and Dick-negative reactors. It therefore appears that whether the organism survives in the throat does not depend on the level of antitoxin present. Whether illness does develop apparently depends on the presence or absence of antibacterial immunity. The subsequent clinical character of the infection, however, is determined by the level of antitoxic immunity. Thus, Schwentker and his co-workers<sup>110</sup> have found that 90 per cent of their patients with tonsillitis were Dick negative, whereas 32 of the 34 persons who developed scarlet fever had positive reactions.

It is now recognized that the toxic component of the streptococcus is responsible for the enanthem, exanthem and constitutional reactions found in scarlet fever, characterized by vomiting, generalized lymphadenopathy, arthralgia and albuminuria. Although precise information is lacking, there is no incontrovertible evidence that persons with a negative Dick test are less likely than others to develop septic complications following streptococcal infections. To establish this point definitely it would be necessary to observe an epidemic of scarlet fever and tonsillitis caused by the same type of streptococcus. Although this was done by Schwentker and his co-workers,<sup>110</sup> they gave no clinical description of their cases. Stebbins, Ingraham and Reed<sup>115</sup> found that complications following a milk-borne epidemic of streptococcal pharyngitis (and hence presumably caused by the same type) were as frequent in those with a rash as in those without one. Hobson<sup>116</sup> concluded that complications were even more frequent when a rash was absent.

The Dick test should probably always be controlled with heat-inactivated toxin, since pseudo-reactions occur as they do with the Schick test. But the Dick-test material dispensed commercially contains no control material, since it is thought that if broth filtrates of high toxin content are used the protein elements will be sufficiently diluted in the final test material to eliminate the false reactions. It is believed that the pseudoreactions are due to streptococcal protein and are unrelated to the toxin. Unlike the true Dick reaction and like the pseudo-Schick reaction, it is more frequent with advancing age and is found oftener in communities where scarlet fever is or has recently been epidemic.

The Dick test is performed by injecting 0.1 cc. of toxin intradermally into the volar surface of the forearm. The reaction is read in twenty-four hours. An area of erythema measuring at least 1 cm. is

\*The reverse of this test is the Schultz-Charlton phenomenon, in which the intradermal injection of immune serum blanches the rash of scarlet fever.

considered a positive reaction. The skin-test dose has been established by the Scarlet Fever Committee as representing the least amount of toxin to which all susceptible persons react positively. This has been determined by skin-testing a large number of children of different ages.

#### SKIN TESTS EMPLOYING ANTIGENS OF VIRAL ORIGIN

Despite the fact that the change in dermal sensitivity following infection was first demonstrated with a virus (vaccinia), it has only been in recent years that skin reactions with antigens of viral origin have been employed. Lymphogranuloma inguinale is the only viral disease in which a skin test is now widely employed as a diagnostic aid. Recently, investigators have shown that a dermal reaction may be elicited in persons convalescent from mumps. This test has proved of great aid in determining susceptibility or immunity to mumps. Beveridge and Burnet<sup>117</sup> and Kane<sup>118</sup> have independently shown that dermal allergy can be elicited in persons convalescent from influenza. Whether this reaction can be used to determine susceptibility has not been established. With improved methods for growing viruses in high titer, there is reason to believe that skin reactions will be employed with increasing frequency in viral diseases.

#### *Frei Test*

Frei's<sup>119</sup> introduction of his test in 1925 made possible the exact diagnosis of lymphogranuloma inguinale and demonstrated that a number of conditions previously considered to be unrelated were diverse manifestations of infection with the virus of lymphogranuloma inguinale. As antigen, Frei used heat-inactivated pus obtained from the unruptured buboes of a patient with lymphogranuloma inguinale. Because of the difficulty in obtaining sufficient material and the possibility that other infectious agents are included, as well as the variation in antigen content, the use of pus from human buboes had major limitations that precluded its widespread use.

Following the demonstration that the virus of lymphogranuloma inguinale can be grown on intracerebral inoculation in mice, Wassen<sup>120</sup> introduced the mouse-brain antigen as a substitute for human pus in the performance of the Frei test. Further experience with this material showed that because of the nonspecific reactions obtained, mouse brain was unsuitable for skin testing.<sup>120-122</sup> When Rake and his co-workers<sup>123</sup> grew the virus of lymphogranuloma inguinale in high titer in the yolk sac of the developing chick embryo, the problem of securing a cheap and ready source of virus was solved. Grace and his co-workers<sup>124</sup> showed that this material gave satisfactory and specific dermal reactions in patients infected with the virus of lymphogranuloma inguinale. Further experience has shown the yolk-sac antigen

to be reliable and to be superior to mouse brain in eliciting the dermal response in infected persons.<sup>125, 126</sup> There is some evidence, however, that it may give more false-positive reactions and is less sensitive than human pus.<sup>127-129</sup> The former product is now available commercially under the name of Lymphogranum.

Extensive surveys have shown the Frei test to be positive in a high percentage (90 to 95 per cent) of persons known to have been infected with the virus of lymphogranuloma inguinale.<sup>130-133</sup> In any group of persons picked at random, however, a number with no history or physical signs of the disease react positively to the antigen.<sup>126, 134</sup> This has been explained on the basis of a latent or veiled infection. Although it is true that accidental laboratory infections in those working with the virus have been acquired via the respiratory tract and the skin of the hand,<sup>135</sup> and that such cases may go unrecognized, there is no evidence that this route of infection occurs in the naturally acquired disease. The question therefore arises whether the positive reactions in persons with no history or physical signs of the disease indicate unrecognized infections or are false-positive reactions. Recently attention has been called to the fact that there is a close antigenic relation between the viruses of lymphogranuloma inguinale, psittacosis, meningopneumonitis, trachoma, inclusion blenorhea, and the atypical pneumonia virus of Eaton.<sup>136-138</sup> Positive Frei reactions have been obtained in cases of atypical pneumonia due to Eaton's virus.<sup>137</sup> Favour<sup>139</sup> observed a positive reaction in 1 of 4 cases of ornithosis that he tested. In this case the question of a previous infection with the virus of lymphogranuloma inguinale was eliminated on the basis of the history and physical examination. Although it is true that the incidence of positive Frei reactions is higher in persons exposed to venereal disease who give no history or physical signs of lymphogranuloma inguinale, to establish definitely the specificity of the Frei test the frequency of the occurrence of positive reactions in persons infected with the above viruses should be determined. Until this is done, there is reason to question some of the positive reactions obtained in persons who have had no history or physical signs of infection with the virus of lymphogranuloma inguinale.

There is a great deal of variation in the literature concerning when the Frei test becomes positive following infection. Reports have varied from one week to six months.<sup>140-143</sup> Wassen<sup>140</sup> experimentally infected a number of volunteers and found that the Frei test became positive as early as the sixth day following the appearance of the lesions. Harrop, Rake and Shaffer<sup>135</sup> noted positive reaction as early as five to nine days following the symptoms in accidental laboratory infections. Reversal of the Frei test has been observed in persons who were intensively treated with chemotherapy early in the disease.



Since a positive Frei test persists for years, possibly for life, a positive reaction does not necessarily mean that a given disease under consideration is due to infection with the virus of lymphogranuloma inguinale. Also, a negative reaction does not necessarily mean that it can be ruled out, since unmistakable cases have been reported with negative reactions to potent antigens.<sup>144</sup> In these cases diagnosis may be established by using the so-called "inverted Frei test." In this test pus from the infected patient injected into persons known to be Frei positive induces a positive dermal reaction.

The Frei test is performed by injecting 0.1 cc. of the antigen intradermally in the forearm. A control injection, consisting of the same volume of uninfected chick-embryo material, is performed in the other arm. A positive reaction consists in the presence of an area of infiltration or a nodule measuring

fection, 50 per cent gave positive reactions. That these were not false-positive reactions is shown by the fact that 96 per cent of this group had mumps complement-fixing antibodies. This supports the suspicion based on epidemiologic grounds that inapparent mumps infection is not infrequent. I have observed 1 such case in a laboratory worker who was constantly exposed to mumps virus. She was known to have had no mumps complement-fixing antibodies and was skin-test negative, and hence was considered to be susceptible. Two months after she began working with the virus she complained of general malaise and ill-defined sensations in the left parotid gland. No salivary-gland involvement was discernible at any time. Shortly thereafter she developed complement-fixing antibodies and became skin-test positive.

Since mumps was observed only twice in several

TABLE 1. *Data on Skin Tests Employing Antigens of Bacterial and Viral Origin.*

TEST	MATERIAL EMPLOYED	TIME READ	SIZE OF POSITIVE REACTIONS	INTERPRETATION OF POSITIVE REACTIONS
Tuberculin	P. P. D. or O. T.	48 hr.	Edema and erythema greater than 5 mm.	Previous infection
Brucellergen	Brucellergen	48 hr.	Edema and erythema greater than 5 mm.	Previous infection
Chancroid	Vaccine (heat-killed bacilli)	48 hr.	Edema greater than 8 mm. and erythema greater than 14 mm.	Previous infection
Pertussis	Detoxified agglutinin	15 min. and 24 hr.	Wheal in 30 min. or induration and erythema greater than 10 mm. in 24 hr.	Questionable immunity
Tularemia	Detoxified antigen	48 hr.	Edema and erythema greater than 10 mm.	Previous infection
Francis	Specific pneumococcus carbohydrate	15 min.	Wheal and erythema	Excess circulating antibody
Influenza-bacillus infection	Specific influenza-bacillus carbohydrate	15 min.	Wheal and erythema	Excess circulating antibody
Schick	Diphtheria toxin	48 and 96 hr.*	Edema and erythema greater than 10 mm.*	Susceptibility
Dick	Erythrogenic streptococcus toxin	24 hr.	Erythema greater than 10 mm.	Susceptibility to erythrogenic toxin
Frei	Inactivated lymphogranuloma-inguinale virus	48 hr.	Induration at least 5 or 6 mm.	Previous infection
Enders	Inactivated mumps virus	24 and 48 hr.	Erythema greater than 10 mm.	Immunity

\*There is a great deal of variation in the literature as to what should be considered a minimal positive reaction. There is also variation as to when the test should be read.

at least 5 or 6 mm. in diameter that is present at the end of forty-eight or seventy-two hours. The control reaction should not measure more than 3 mm. If the test is negative at the end of seventy-two hours, it is necessary to examine the area at intervals of several days, since a delayed reaction occasionally occurs.

### Enders Test

Using as antigen a heat-inactivated suspension of the parotid gland of a monkey infected with the virus of mumps, Enders, Cohen and Kane<sup>145</sup> were able to demonstrate the development of dermal hypersensitivity in persons convalescent from mumps. In a systematic survey of almost 300 students at the Harvard Medical School a dermal reaction consisting of an area of erythema measuring at least 10 by 10 mm. was obtained in 96 per cent of those students who had a definite past history of mumps.<sup>146</sup> Of those who denied any previous in-

hundred persons who had a definitely positive skin test (an area of erythema greater than 10 by 10 mm. in twenty-four hours), it is clear that an inapparent infection will produce as solid an immunity as an overt attack. Accordingly, the demonstration of a positive dermal reaction with rare exception means immunity. In the last three years over 1500 skin tests have been performed without unpleasant local or general reactions of any description. Sixty-eight cases of mumps have been recorded in this group. In 57 of these there was either no dermal reaction or its area measured less than 2 by 2 mm. in diameter. In 8 cases areas were observed that ranged between 2 by 2 mm. and 10 by 10 mm. In only 3 cases was the area greater than 10 by 10 mm. If one accepts an area of erythema of 10 by 10 mm. or less as indicating susceptibility, then 95 per cent of those who eventually developed mumps were susceptible as determined by the intradermal test. Of several hundred persons who were found to have

reactions greater than 10 by 10 mm. in twenty-four hours, only 3 developed mumps\*. It is therefore believed that a reaction greater than 10 by 10 mm. with rare exception means immunity against the mumps virus. The intradermal test is of no value as an aid in diagnosis, since the interval when a positive reaction is first observed may vary from several days to three months after the onset of the disease. Once hypersensitivity is established, it apparently persists for life.

Within the last few months the virus of mumps has been grown in the yolk sac of the developing egg embryo. This virus has been reported as giving reliable dermal reactions in immune persons<sup>147</sup>. Should this prove to be so, a cheap and ready source of virus for skin testing should shortly be available.

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The pertinent data on the practical application of the tests discussed in this review are summarized in Table 1.

\*False-negative tests have been observed in about 2 per cent of the persons considered to be immune on the basis of positive complement-fixation tests

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 31261

#### PRESENTATION OF CASE

A thirteen-month-old boy was admitted to the hospital because of the sudden appearance of a mass on the right side of the neck.

The child had been well until five weeks before admission, when he awakened one morning crying more than usual. The mother sensed that something was wrong, but the temperature was normal. At 11:00 a.m. the temperature had risen to 104°F. and the child was rushed to a hospital. A diagnosis of early pneumonia was made. He was given sulfadiazine, and the temperature returned to normal in two days. On the third hospital day an orange-sized mass suddenly appeared on the right side of the neck. This was aspirated, and the neck again appeared normal. X-ray examination demonstrated a mass in the upper mediastinum pressing on the trachea. There was no discharge from the site of aspiration, and no return of the swelling in the neck. On the seventeenth hospital day the child was discharged to his home, asymptomatic. Approximately two weeks later, with no recurrence of complaints, he was admitted to this hospital for further study.

The child had been delivered at term with no difficulty and without forceps. The birth weight was 7½ pounds. He was breast fed for only one week and thereafter, until eleven months of age, was maintained on an evaporated milk Dextrimaltose formula, adequately supplemented with vitamins. At one year he weighed 25 pounds. One week before the onset of the present illness he had one injection of diphtheria-tetanus toxoid.

Physical examination revealed a well nourished boy who was well developed for his age. He had a lusty cry and no apparent respiratory difficulty. He weighed 25½ pounds and measured 75 cm. in length. The skin was normal. The pupils were normal and reacted to light. Four incisors above and below, and a right lower premolar were present. There was abnormally profuse drooling of saliva from the mouth. The right side of the neck just above the clavicle was fuller than the left. A blunt, soft, smooth, oval, nontender mass about 4 cm. in diameter lay anterior to and appeared to merge with the right sternocleidomastoid muscle. This mass

was thought not to move with swallowing. It presented no bruit or pulsation. The lungs were clear except for a few fine crepitant rales over the right upper lobe. The heart had normal position, size, rate, rhythm and sounds. The abdomen and extremities were normal.

The temperature, pulse and respirations were normal. The blood pressure was 105 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 4,200,000, with 12.2 gm. of hemoglobin, and a white-cell count of 13,600, with 70 per cent neutrophils, 28 per cent lymphocytes and 2 per cent monocytes. The urine was normal.

An x-ray examination of the chest showed a homogeneously dense mass in the right upper posterior chest that measured approximately 4 by 4 cm. in diameter (Fig. 1). It displaced the trachea to the right and anteriorly. There was no definite evidence of collapse of the upper lobe. The vertebral bodies and ribs showed no evidence of erosion. The heart shadow appeared to be normal. A barium swallow during fluoroscopy showed the esophagus to be displaced to the left by the mass both above and below the manubrium. Whether the esophagus was displaced backward or forward could not be determined.

The temperature, pulse and respirations and the appearance of the neck remained unchanged. The blood was grouped and crossmatched, and on the fifth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. NATHAN B. TALBOT: One may introduce the discussion of this case by commenting that, with the information at hand, it is not going to be possible to make anything more than a tentative diagnosis. Had we been given information concerning the nature of the fluid aspirated from the mass in the neck, it might have been easier to make a reasonably accurate diagnosis. Had the fluid removed when the child was seen first been replaced by some radio-opaque material, such as iodide solution, valuable information concerning the size, connections and geography of the mass might have been obtained. Transillumination of the cervical mass at that time might have been helpful, for it should have distinguished between blood and clear fluid. It would also have been of interest to know whether the cervical mass was reduced by gentle pressure and whether such a procedure prompted a change in the size of the thoracic mass. In other words it may be possible to make a fairly accurate pre-operative diagnosis in such cases as this if advantage is taken of relatively simple procedures. Despite the paucity of information, certain possible diagnoses may be considered.

It seems probable that the mass in the neck was cystic, that the mass in the thorax was part of the same structure and that the mass was present prior

\*On leave of absence.

to the episode of pneumonia, which perhaps through some mechanism induced a sudden increase in its size and hence called attention to its presence. It appears from the history that this lesion had not interfered seriously with the development of the child, since the measurements recorded are normal for an infant of his chronologic age. There was little to suggest that the process was inflammatory, since the temperature and pulse were not strikingly abnormal, and there was only a slight leukocytosis. Incidentally, no tuberculin test is recorded.

It is in this age group that congenital malformations frequently make themselves known. Of the cystic swellings of congenital origin that present in

DR. SCHULZ: At least some of it lies posteriorly and displaces the trachea anteriorly as well as to the left, and one may assume that it arises outside the lung rather than in it.

DR. TALBOT: Can you see continuity of the mass in the chest with that of the neck?

DR. SCHULZ: It is difficult to be sure about the mass in the neck; there is no demarcation between the visible mass and any mass that may be present in the neck, for it is the same density as the normal soft-tissue structures of the neck.

DR. TALBOT: There are no sharp outlines and no shadows suggestive of teeth, bone or anything of that sort?



FIGURE 1. Roentgenogram of Chest.

the anterior cervical triangle, branchial-cleft cysts and thyroglossal-duct cysts may be mentioned. Had the swelling presented in the posterior cervical triangle these could have been almost automatically ruled out. Although they cannot be completely discarded in the present case, I believe that they are unlikely diagnoses because of the fact that the cervical mass probably extended into or took origin in the posterior mediastinum. Incidentally, the mass did not move on palpation, which rules further against a thyroglossal duct.

May we look at the x-ray films?

DR. MILFORD D. SCHULZ: Here you see this rather sharply outlined mass in the right upper chest displacing the trachea anteriorly and to the left.

DR. TALBOT: Can we say it is a posterior mediastinal mass?

DR. SCHULZ: No.

DR. TALBOT: If we assume that there was a posterior mediastinal mass, not apparently of pulmonary origin or at least not seriously impairing upper or lower respiratory function, we can discard the possibility of lung cyst. We are left with certain other possibilities.

The first of these is cystic hygroma, which is a cystic overgrowth of lymph channels due to a developmental disarrangement of the tissues. It often originates in the neck and may extend upward toward the ears or jaw or downward into the chest.<sup>1</sup> This diagnosis cannot be ruled out.

Secondly, one might consider the presence of a teratoma of mediastinal origin. These usually have a dense wall and occasionally show areas of calcification, although I gather they are less likely to

do so in this region than in other parts of the body.

The mass might have represented cystic degeneration of a variety of mediastinal tumors. It is said, however, that in such a lesion there is often some remaining solid and hence palpable tissue, which gives a clue to the diagnosis. No solid tissue was described in the present case.

Next the possibility arises that the mass was an arteriovenous aneurysm. The only finding in favor of this diagnosis is the blood pressure, which was slightly to moderately elevated. On the other hand the heart was of normal size, which rules quite strongly against this diagnosis. It also seems most unlikely that blood was aspirated from the mass, since no mention of such a potentially important fact was made. A deeply seated hemangioma would also yield blood on aspiration.

There remains one other interesting possibility, an esophageal duplication or mediastinal cyst of enteric origin.<sup>2</sup> These may be silent for a period of time but are usually recognized during infancy. Cough, dyspnea, cyanosis and recurrent or chronic pneumonia are the usual presenting complaints and when present are due to pulmonary compression. Dysphagia and regurgitation of feedings occur when there is impingement on the esophageal lumen. In this connection it is of interest that the child was said to drool abnormally. Although this seems an extraordinary remark when applied to an infant of this age, it may have been inserted to provide us with a clue or — and such would not be unique in these meetings — as a sort of red herring. Incidentally, pain such as this patient apparently had at the onset of the illness may be caused by distention of the walls with suddenly increased intracystic pressure. In such cystic structures, infection such as this patient had may in some manner lead to obstruction of the normal lymph channels, with consequent rapid enlargement. Finally, the x-ray findings are characteristic of a posterior mediastinal tumor or cyst. Fluoroscopy, as in this patient, shows no fistulous connection. Although they occasionally erode the vertebrae, there was no evidence of that here.

In conclusion it is fair to say that the most important point in such a case as this is that surgical exploration should be carried out for the purposes both of an accurate diagnosis and of potentially corrective procedures. I should place mediastinal cyst of enteric origin as my first choice, and cystic hygroma as my second.

DR. BENJAMIN CASTLEMAN: Dr. Sweet, you operated on this child. Will you describe your findings?

DR. RICHARD H. SWEET: This was an amazing tumor in many ways. My preoperative diagnosis was a cyst of enteric origin, the so-called "reduplication" that Dr. Ladd talks about. I know enough about mediastinal tumors to appreciate that one can rarely make an accurate diagnosis ahead of time.

The fluid aspirated from the cyst within the neck was reputed to have been clear. That information obviously was not in the case history as presented.

The tumor was filled with cystic loculations, which contained watery fluid. It was an enormous tumor, considering the size of the child. Anatomically it covered a large surface, and in freeing it we disclosed a great many structures. The operation was a lesson in anatomy. It extended to the azygos vein and right main bronchus. Posteriorly it was necessary to denude the first and second ribs, the actual rib periosteum being removed with the tumor. It was an adherent tumor, and in taking it out we exposed and divided the first intercostal nerve and the highest intercostal artery, which are rarely seen. When we dissected the tumor medially we found that, although it was not an invasive tumor, it at least had surrounded all the structures and had grown around the innominate vein and innominate artery. In order to get the subclavian artery and other structures away from it I had to incise the tumor and peel it off one side one way and the other side another way. In doing that I exposed the right vagus nerve and the right recurrent laryngeal nerve and the cords of the brachial plexus as they crossed over the first rib. It was also adherent to the esophagus, and there was a portion of it that extended to the left behind the heart and great vessels, which I did not get. There was a portion within the neck, which I could not possibly remove because it had grown around all the structures there and I could not dissect beyond the confines of the superior portion of the chest.

#### CLINICAL DIAGNOSIS

Mediastinal cyst of enteric origin.

#### DR. TALBOT'S DIAGNOSIS

Mediastinal cyst of enteric origin.

#### ANATOMICAL DIAGNOSIS

*Hygroma colli cysticum.*

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Sweet has outlined extremely well the gross penetrating character of the tumor. Microscopically this same feature was evident. The tumor was composed of multilocular cystic spaces of varying sizes, all of which were lined with flattened endothelial cells, namely, the structure of lymph vessels. It was then a true cystic hygroma, which is a form of lymphangioma and apparently arises from lymphatic rests, derived from the jugular lymph sac. Scattered in between some of the cystic spaces were many large nerves and blood vessels, which were apparently being surrounded and engulfed. This appearance is in keeping with Goetsch's<sup>3</sup> exhaustive study of these hygromas. He showed that they grow and propagate by the sprouting from the cyst walls of endothelial-lined membranes that

continue to secrete and form more cystic spaces, and so on. As it continues to grow, it engulfs muscles, nerves and blood vessels, which accounts for the operative findings in this particular case. In Goetsch's series of 12 cases most of the tumors were in the neck and had not invaded the mediastinum. He also made the statement that the prognosis is poor in those cases in which the tumor goes down in the mediastinum. One case in his series responded well to x-ray treatment, so that perhaps it would be worth while to give the patient postoperative x-ray treatment.

DR. SWEET: It was obvious to me when I had exposed the tumor and had begun the dissection that it was one that could not be totally removed.

DR. TALBOT: What was the postoperative course?

DR. SWEET: The patient made an excellent recovery and went home. The only evidence of the operation, except for the scar, is that he has a Horner's syndrome.

DR. CASTLEMAN: But you expected that after the operation.

DR. SWEET: Yes; I wrote it in my operative note that I had interrupted the sympathetic chain, the intercostal artery and the first intercostal nerve.

DR. SCHULZ: When giving x-ray treatment it should be borne in mind that one might destroy the epiphyseal growth in a child of this age.

DR. CASTLEMAN: Has the child any symptoms of a mediastinal tumor?

DR. SWEET: No.

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#### CASE 31262

##### PRESENTATION OF CASE

A seventy-two-year-old man was brought to the hospital because of hematemesis, tarry stools and a loss of consciousness.

About fifteen years before entry the patient began to suffer financial reverses and developed abdominal symptoms, which were attributed to a peptic ulcer. Ten years before admission he was treated at another hospital for a bleeding ulcer. He followed the prescribed diet sporadically and acquired such poor eating habits that four years later he was again admitted because of quite marked skin and other systemic changes consistent with severe nutritional deficiency. He responded well to an improved dietary regime but continued with periodic and vague epigastric symptoms, which included mild distress and a feeling of marked gaseous distention after meals. Four years before admission he passed

tarry stools for two weeks. He was treated at home with bedrest and a bland diet. From then until the time of admission to this hospital he had continued on a fairly well supervised, bland diet. Three and a half years before entry a gastrointestinal series showed a constant deformity at the base of the duodenal cap near the pyloric sphincter, with an ulcer at this point measuring 6 mm. in its greatest diameter. Another gastrointestinal series a month later showed some decrease in the size of the ulcer. A year later, or two years before admission, another gastrointestinal series showed a small 1-mm. ulcer niche, which was probably on the lesser curvature side at the pylorus. There was some deformity of the duodenal cap. Three days before admission he vomited a cupful of coffee-grounds fluid and began to have loose tarry stools, with increased epigastric pains. On the day of entry he fainted shortly after complaining of pain in his left leg. On regaining consciousness he complained of weakness and cold perspiration. Six years before admission he began having pain in the arms radiating to the shoulders. These pains came on when he walked in a cold wind or at the onset of any exertion. When severe this pain was promptly relieved by nitroglycerin. At that time the blood pressure was 158 systolic, 100 diastolic. Four years before admission he complained of substernal oppression on exertion, with less pain in the arms and shoulders. The blood pressure was 145 systolic, 85 diastolic. During the four years before admission, the substernal pains varied in frequency and severity. They were worse in cold, damp or extremely hot weather. Nitroglycerin for severe pains and barbiturate sedation continually afforded considerable relief. A long blowing systolic apical murmur was unchanged during the six years before entry. The heart size was consistently thought to be on the upper limit of normal by percussion and auscultation. The pulse was 75 to 80 and regular, and the blood pressure was quite constant at about 140 systolic, 80 diastolic. An electrocardiogram three months before admission showed a normal rhythm with a rate of 85, sagging ST<sub>1</sub> and ST<sub>2</sub>, inverted T<sub>1</sub>, diphasic T<sub>2</sub>, low upright T<sub>3</sub>, wide slurred QRS complexes measuring 0.14 to 0.16 second, occasional ventricular premature beats, deep S<sub>2</sub>, small R in Leads CF<sub>2</sub> through CF<sub>4</sub>, notched or bifid upright QRS in Lead CF<sub>5</sub>, upright T waves in Leads CF<sub>2</sub> through CF<sub>4</sub> and inverted T waves in Lead CF<sub>5</sub>.

Physical examination revealed a well developed, fairly well nourished man. The chest was moderately emphysematous. The skin was pale, cold and clammy. He was stuporous but was able to obey commands. There was a sagging but not a complete paralysis of the left face, and no apparent paralysis of the extremities. The lungs were clear. No heart sounds could be heard. The heart was not enlarged to percussion. The abdomen was soft, slightly tympanitic but not markedly distended; peristalsis

was diminished. The liver and spleen could not be felt.

The temperature was normal, the pulse not obtainable, and the respirations were 25. The blood pressure was not obtainable.

Examination of the blood showed a red-cell count of 1,960,000. After two whole-blood transfusions the red-cell count was 3,600,000, and the white-cell count 10,700, with 66 per cent neutrophils. A glove specimen of stool was tarry and gave a +++ guaiac test. Blood drawn after the transfusions showed a serum nonprotein nitrogen of 94 mg. per 100 cc., a fasting blood sugar of 137 mg. and a protein of 6.4 gm.

During the first twenty-four hours the blood pressure was periodically obtainable and rose on one occasion to 85 systolic, 50 diastolic. After the first twenty-four hours, despite whole-blood transfusions, the blood pressure was only rarely obtainable, reaching 100 systolic, 65 diastolic, on one occasion. The pulse was extremely weak when obtainable and remained between 80 and 100. During the first twenty-four hours he complained of epigastric and low substernal pain. He had no bowel movements and did not vomit. A Levine tube afforded relief from gaseous distention and abdominal discomfort. It brought up a small amount of blood in about 500 cc. of thin gastric contents. The urine gave + to ++ tests for albumin; the sediment showed an occasional red and white cell and a few hyaline casts.

Early on the second day the patient was digitalized with Cedilanid. An electrocardiogram a few hours later showed normal rhythm, at a rate of 120, a PR interval of 0.22 second, inverted T<sub>1</sub>, upright T<sub>2</sub> and T<sub>3</sub> with slurred QRS complexes that measured 0.12 second, small R and deep S waves in Leads CF<sub>1</sub> through CF<sub>4</sub> and upright wide QRS in Lead CF<sub>5</sub> with inverted T waves. The blood pressure and pulse were again not obtainable near the end of the second day. The lungs were filled with rales, and the liver was enlarged.

The patient became cyanotic and comatose and expired quietly approximately forty-eight hours after admission.

#### DIFFERENTIAL DIAGNOSIS

DR. DAVID HURWITZ: We are dealing with an elderly man whose history points to both severe gastrointestinal and cardiovascular disease. He had had ulcer symptoms for fifteen years and gastrointestinal bleeding off and on for ten years. X-ray confirmation of the ulcer was obtained three and a half years before entry, and subsequent x-ray examination showed evidence of healing. The last gastrointestinal series, two years before admission, demonstrated the presence of an ulcer that seems to have been in a somewhat different location than the one originally described. Are these films available?

DR. MILFORD D. SCHULZ: This 5-mm. fleck probably represents the ulcer crater that was described; it appears to be in the base of a severely deformed duodenal bulb, but it is difficult to be certain where the pylorus is. On the examination a month later the crater is slightly smaller. On the last examination a quite small ulcer is seen that occupies a position comparable to that previously described.

DR. HURWITZ: For the final two years there is no record of further gastrointestinal bleeding or distress until three days before entry, when he vomited blood and passed tarry stools. I think that the evidence for a bleeding peptic ulcer is excellent. The long duration of the recurrent hemorrhages and the x-ray evidence make ulcer by far the best possibility. The duration, x-ray findings and apparent freedom of significant symptoms for two years are certainly against neoplasm. There is also nothing pointing to bleeding esophageal varices.

In addition to the ulcer symptoms he had a six-year history of exertional substernal pain relieved by nitroglycerin. I think that we may call this angina without much question. "Pain in the arms radiating to the shoulders" is unusual, but later the symptoms became more typical. The blood pressure was not remarkable for his age. The electrocardiogram showed definite evidence of myocardial disease. From the description, I take it that he had left bundle-branch block. From the history and electrocardiogram, then, we can say that he had coronary heart disease.

On admission, he appears to have been in shock. His face showed "a sagging but not a complete paralysis of the left face." It is difficult to ascribe much significance to this in such an acutely ill patient. There is no further mention of pain in the leg. I assume that it did not recur. Apparently he remained in shock until death, in spite of transfusions.

The positive laboratory findings are, first, a severe anemia, which was improved by transfusions, and, secondly, an elevated nonprotein nitrogen. The latter is a frequent finding in cases of severe bleeding into the gastrointestinal tract. It occurs within twenty-four hours of the bleeding and, when markedly elevated, is considered to be a poor prognostic sign. Whether the elevation of the nonprotein nitrogen is due solely to absorption of blood from the intestinal tract or to the effects of acute blood loss, dehydration, shock and poor renal function is not clear. Perhaps a combination of all these factors is present. A blood sugar level of 137 mg. per 100 cc is ordinarily suggestive of diabetes but is not particularly significant in an elderly patient in shock who possibly was given some intravenous glucose with his transfusions during the preceding night. The urinary findings are consistent with what one would expect in a patient in shock. The electrocardiogram after Cedilanid shows a prolonged PR and a prolonged QRS, although the latter was

shorter than it was before entry. These findings are indicative of coronary disease, without pointing toward an acute process.

Severe hemorrhage from an ulcer that has eroded a sclerotic vessel can produce the major clinical picture alone. No added condition is necessary. It is interesting, however, to speculate on what effect, if any, the severe hemorrhage had on his coronary heart disease. It is known that severe blood loss may further increase coronary insufficiency and may result in irreversible myocardial changes, which, if of sufficient duration, may result in myocardial infarction. Is there any evidence of this having occurred here? He did have substernal pain after entry, but it was low and associated with epigastric pain that occurred before his collapse and was probably due to the ulcer. The final electrocardiogram did not give any evidence of an acute process, although it was taken early and the patient was in shock. It is quite possible that he had a fresh infarction on the basis of pre-existing coronary disease and shock, but I cannot make the diagnosis on the available data.

It is difficult to evaluate the history of pain in the left leg before entry. Leg pain followed shortly by collapse and subsequent substernal and epigastric pain suggests a dissecting aneurysm. The lack of antecedent hypertension, the absence of severe chest or back pain and the short duration of the leg pain, however, are against this diagnosis. Usually in this condition the blood pressure remains high after dissection takes place, and a few cases present the picture of collapse without pain. On the whole, it is not likely that the patient had a dissecting aneurysm, and I prefer to leave the leg pain unexplained.

In summary, then, I should say this patient had severe gastrointestinal bleeding from a duodenal ulcer, which had probably eroded a sclerotic vessel. This alone can explain practically the whole picture. In addition, this patient had had clinical evidence of coronary heart disease for some time before the onset of the hemorrhage. The shock might have been responsible for a fresh myocardial infarction, but we have no clinical evidence for it.

DR. BENJAMIN CASTLEMAN: Dr. Williams, have you anything to add?

DR. CONGER WILLIAMS: Bundle-branch block often obscures changes in the electrocardiogram that have been produced by myocardial infarction. This is especially true in left bundle-branch block complicated by anterior myocardial infarction, because both conditions result in the loss of R waves over the precordium in Leads 1 to 4. Sometimes the diagnosis can be made by observing serial changes in the T waves. In this case the electrocardiogram does not help in making the diagnosis beyond indicating likely damage to the coronary circulation, which could have been chronic.

DR. CHESTER M. JONES: A high nonprotein nitrogen level is always interesting when associated with hemorrhage. It is important, however, not to lay too much stress on it. It was believed for some time that a high nonprotein nitrogen associated with hemorrhage, as Dr. Hurwitz has pointed out, is a bad prognostic sign. It actually does not work out that way. We have seen them even higher than this and the patients do well.

#### CLINICAL DIAGNOSES

Duodenal ulcer, bleeding.  
Coronary heart disease.  
Coronary thrombosis, recent?

#### DR. HURWITZ'S DIAGNOSES

Duodenal ulcer, with erosion of sclerotic vessel and hemorrhage.  
Coronary heart disease, possibly with recent myocardial infarction.

#### ANATOMICAL DIAGNOSES

Peptic ulcer, bleeding.  
Coronary thrombosis, recent and old.  
Myocardial infarction, early and old.

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy findings were almost exactly as Dr. Hurwitz predicted. This man had a peptic ulcer that bled before he came into the hospital. There was evidence that the bleeding had stopped while he was in the hospital, because we found no blood in the stomach. There was, however, old blood throughout the intestinal tract. The ulcer involved the pylorus.

The heart weighed 500 gm. and showed severe sclerosis of the coronary arteries, such as one sees in patients with angina. There was an old occlusion of the right coronary artery, which must have occurred years previously, with resultant scarring of the posterior wall of the left ventricle. In addition there was a terminal acute coronary thrombosis in the left descending artery and an associated acute anterior myocardial infarction. The myocardium showed acute degeneration of the fibers with polymorphonuclear infiltration, the picture that one sees in the early stages of myocardial infarction.

DR. JONES: Was there arteriosclerosis of the arteries in the leg, which caused the pain?

DR. CASTLEMAN: He had generalized arteriosclerosis. There were no thrombi in the leg veins and no evidence of pulmonary infarction.

There was also an extensive terminal bronchopneumonia, which must have occurred during the last day or two. The final blow was the coronary thrombosis.



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## PROPHYLAXIS AND TREATMENT OF GAS GANGRENE

THERE was a great deal of optimism in the earlier part of the war about the relatively small number of cases of gas gangrene encountered in the various theaters where the British and American troops were operating. It was assumed that the widespread use of sulfonamide drugs locally and systemically was responsible for the low morbidity from this disease. Experimental studies on the use of these drugs in the prevention of infection in animals also served to strengthen this belief. As the fighting moved into European countries, however, cases of gas-gangrene wound infection have become of increasing importance.<sup>1</sup> The problem has been re-

viewed by the Medical Research Council in England,<sup>2</sup> and has been brought up to date more recently in a supplement of the *Army Medical Department Bulletin* issued by the British War Office.<sup>3</sup> Most of the significant clinical features of this condition are brought out in the latter publication, including some that are not widely appreciated. Recommendations are also given for the use of sulfonamides, penicillin and antitoxins, both for prophylaxis and for the treatment of established infections. These recommendations are based on recent experiences. A few excerpts from this bulletin and a résumé of the recommendations for treatment should be of interest to American readers.

Gas gangrene (clostridial myositis) may be defined as an infection of muscle with anaerobic bacteria of the genus *Clostridium* (particularly, *Cl. welchii*; *Cl. oedematiens* and *Cl. septicum*), whose common habitat is in soil and in the intestines of many animals. These organisms produce powerful toxins which, by their necrotizing action, favor the local spread of infection and by their wider dissemination in the body rapidly produce a profound and shock-like toxemia. The mere finding of anaerobic bacteria in a wound of muscle is of little significance; in warfare over cultivated ground almost every wound will be so contaminated. In contrast to simple contamination, anaerobic infection of muscle is a true myositis, always acute and usually diffuse. Sometimes only a single muscle is involved, but as a rule whole muscle-groups are affected. The disease is extraordinarily acute, and can rapidly spread through an entire limb. It is this fulminating course that makes gas gangrene so dangerous, and renders its early and accurate diagnosis of such extreme importance.

The essential features in its prevention and treatment are the elimination of the bacteria by excision of the infected tissues and by chemotherapeutic drugs, and the neutralization of the toxins by the administration of antitoxins. The disease has a very high death-rate unless it is promptly diagnosed and properly treated. . . .

Gas gangrene can follow quite trivial injuries, but is most likely to develop where the wound is associated with the following features: interference to the main blood-supply of a limb; extensive laceration of muscle, particularly of the thigh, buttock and shoulder; compound fractures of the long bones, especially [those] of the lower limb; foreign bodies, clothing or dirt carried deeply into the tissues; prolonged application of a tourniquet, or tight packing; application of a tight plaster or even a tight dressing to an inadequately excised wound; delay in surgical treatment.

In the prophylaxis of gas gangrene it is recommended that the following measures be taken as soon as possible after infliction of the wound: one ampule containing 22,500 units of polyvalent gas-gangrene antitoxin should be immediately injected intravenously or intramuscularly, preferably by the

former route, together with the usual dose of tetanus antitoxin\* (if there is a delay of more than twenty-four hours, 45,000 units—two ampules—should be given); sulfonamide drugs should be administered both locally and systemically (the British also include a 1 per cent suspension of finely powdered proflavine in sulfathiazole for local use, but the efficacy of all local chemotherapy has been questioned by American surgeons); adequate wound excision should be provided (this is the most valuable prophylactic measure and should *never* be unnecessarily delayed).

In the treatment of established gas gangrene, surgical measures are combined with antitoxin and drugs, speed being essential to the saving of life. Preoperatively it is recommended that 67,500 units (three ampules) of polyvalent gas-gangrene antitoxin, or 112,500 units (five ampules) if toxemia is severe, be injected, preceded or accompanied by sulfathiazole (sulfadiazine would probably be preferred in this country). The soluble form of the latter may be given subcutaneously in salt solution or intravenously either in saline or in distilled water (it is important not to give sodium salts of sulfonamide drugs in the same apparatus used for blood transfusion since clots may form). Transfusions of whole blood are advised unless particularly contraindicated. Pentothal, followed by nitrous oxide and oxygen (40 to 50 per cent), is recommended for anesthesia. Anoxia should be guarded against during the inhalation anesthesia.

Removal of the infection by complete excision of the affected tissues is essential. Amputation is by no means a routine necessity, though frequently inevitable because of vascular damage. Where only one muscle or one group of muscles is involved, that muscle or muscle-group should be extirpated from origin to insertion. An ample exposure is necessary, and great care must be taken not to damage the blood supply to adjacent muscles. . . .

If radical surgery is impossible, either because of the site of the infection or the condition of the patient, the muscle-sheaths and muscles should be freely incised to relieve tension, and intensive therapy with antitoxin and drugs pursued. Where a limb is involved, it is frequently of advantage to apply a tourniquet proximal to the upper limits of infection in order to establish a "physiologic amputation."

For local chemotherapy it is recommended that the wound should be washed out if necessary with a 0.1

per cent solution of proflavine and then frosted with a sulfonamide.

Penicillin therapy is also recommended. The initial dose (30,000 units) is given intramuscularly on the operating table or earlier. This is followed either by a slow intravenous drip at the rate of 5000 or 6000 units per hour for twenty-four to forty-eight hours or by the injection of 15,000 units every three hours. Larger doses, up to 25,000 units every two hours, are probably preferable.

It is best to give blood transfusions and glucose-saline infusions by drip during the following twenty-four to forty-eight hours. Antitoxin administration is continued so long as signs of toxemia remain. A dose up to 60,000 units, repeated every four to six hours, may be given by intravenous injection in a small volume. The reduction in the pulse rate is taken as evidence of diminishing toxemia. Sulfonamide therapy is continued by parenteral route so long as necessary and orally thereafter, adequate amounts of alkali being given and the fluids being adjusted to avoid renal complications.

It is of interest that Dowdy, Sewell and Vincent,<sup>4</sup> on the basis of extensive studies on gas-gangrene infection in experimental animals, have also come to the conclusion that all these measures should be used.

With respect to sulfonamide treatment, interest has recently centered about the German preparation known as Marfanil. This compound is 4-aminomethyl-benzene sulfonamide and is of particular interest because its action is said not to be inhibited by *p*-aminobenzoic acid, serum or pus. Although the compound has been known in this country for at least three years, it did not receive much attention until it was found by the British among German supplies captured in North Africa.<sup>5, 6</sup> Marfanil is highly soluble and, in preliminary clinical trials, appears to be somewhat more effective than the earlier preparations for local use in the prevention and treatment of anaerobic wound infections. These findings have not been widely confirmed, nor is the toxicity of the compound well understood. When given by mouth it apparently is no more effective than sulfanilamide. Further studies of this compound and related ones would be of interest, but since the use of penicillin is now occupy-

\*The British Medical Corps still recommends the routine prophylactic use of tetanus antitoxin in spite of the fact that many British soldiers have been immunized with tetanus toxoid.

ing the attention of most workers, the clinical trial of these chemicals outside Germany will undoubtedly be delayed.

That considerable difference of opinion exists concerning the prevention and treatment of gas gangrene is evidenced by a recent directive issued by the War Department.<sup>7</sup> This bulletin does not recommend the prophylactic use of gas-gangrene antitoxin and questions its therapeutic value, except the employment of trivalent serum, containing *Cl. oedematiens* antitoxin, in cases of the "wet" type of infection. Furthermore, although the administration of sulfonamides and penicillin is advised, it is stated that any form of chemotherapy probably does little more than to prevent the spread of infection. Chief reliance is placed on proper surgical management.

### REFERENCES

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6. Evans, D. G., Fuller, A. T., and Walker, J. New drugs in chemotherapy of experimental gas gangrene. *Lancet* 2:523-527, 1944.
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## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

COX — Oscar F. Cox, M.D., of Brookline, died June 3. He was in his fifty-eighth year.

Dr. Cox received his degree from Tufts College Medical School in 1914. During World War I he served with the Army overseas. He was a member of the staff of Massachusetts Memorial Hospitals and the Boston Dispensary. He was chief of the Genitourinary Clinic at Boston Dispensary, director of the Division of Genitoinfectious Diseases at Massachusetts Memorial Hospitals, chairman of the Advisory Committee on Venereal-Disease Control of the Massachusetts Department of Public Health, director of the Massachusetts Society for Social Hygiene, secretary of the American Neisserian Medical Society and a member of the Subcommittee on Venereal Diseases of the National Research Council. He was clinical professor of urology at Tufts College Medical School and associate professor of medicine at Boston University School of Medicine. He was a fellow of the American Medical Association.

His widow, his mother, a son and a daughter survive.

WHELAN — Charles Whelan, M.D., of North Cohasset, died May 29. He was in his sixty-ninth year.

Dr. Whelan received his degree from Tufts College Medical School in 1905. He was among the first sixteen of its graduates to enlist in the medical corps during World War I, and organized the x-ray department at the debarkation hospital in New York where 38,000 casualties were treated. He had been chief radiologist at the Quincy City Hospital for several years and was consultant in roentgenology at the Carney Hospital and New England Hospital for Women and Children. He was a member of the American Board of Radiology, the New England Roentgen Ray Society and the Radiological Society of North America and a fellow of the American Medical Association.

His widow and two daughters survive.

## NEW HAMPSHIRE MEDICAL SOCIETY

### DEATH

SMITH — Henry O. Smith, M.D., a lifelong practitioner in Hudson, died suddenly on May 14, 1945, just after he had completed a visit at a patient's home in Londonderry. He was born in Hudson on December 18, 1864, graduated from Dartmouth College in 1886 and received his medical degree from Bellevue Hospital Medical College in 1887. He started practice in Hudson in 1888 and for the past fifty-seven years had continued the practice of medicine there.

Dr. Smith was a member of the county and state medical societies, having served as speaker of the House of Delegates of the New Hampshire Medical Society in 1925-1926, as president of the state society in 1929-1930 and as a member of the Board of Trustees from 1933 to 1942, when he was elected trustee emeritus.

He was presented the Gold Medal of the state society for fifty years' membership at the meeting in 1938, and that same year he was honored at a testimonial dinner by his townspeople, who presented him with a suitably engraved watch "in appreciation of fifty years of faithful service."

Dr. Smith was a member of the Hudson Baptist Church, Hudson Grange, New Hampshire Historical Society and New England Historical Genealogical Society.

A number of years ago he wrote the history of the Baptist Church of Hudson, and in 1927 he compiled and published *The Early Story of Hudson, New Hampshire*. He served as chairman of the committee to formulate plans for the observance of the one hundred and fiftieth anniversary of the New Hampshire Medical Society. Along with this work, he edited, amended and brought up to 1941 *The Story of the New Hampshire Medical Society*, which originally had been written, including the facts up to 1854, by Dr. L. Bartlett How. This was printed and distributed to the members of the state society.

Dr. Smith is survived by one son, Dr. Deering G. Smith, of Nashua, two grandchildren and one sister.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### NEW TYPE STANDARD DEATH CERTIFICATES

Under the General Laws, Chapter 46, Section 10, a physician or officer furnishing a death certificate shall insert a recital and specify the war, if the deceased is a veteran.

Secretary of State Frederic W. Cook has directed that there be printed on the reverse side of the Standard Death Certificate the following:

Date of entering military service  
Date of discharge  
Rank, rating  
Organization, outfit and service number

Dr. Vlado A. Getting, commissioner of the Massachusetts Department of Public Health, has called to the attention of the boards of health of the Commonwealth that the Standard Death Certificate is not complete until the data called for, as to the veteran, is recorded thereon.

## PENICILLIN FOR TREATMENT OF GONORRHEA

Penicillin is now available without cost to all physicians of the Commonwealth for the treatment of gonorrhea.

Physicians are requested to submit a report of the case of gonorrhea on the form supplied by the Massachusetts Department of Public Health for that purpose. A supply of these forms will be sent on request.

Two bottles of penicillin, each containing 100,000 Oxford units, may be requested for each case. Directions for administration of the penicillin are enclosed with each bottle.

Points of distribution outside of the Metropolitan Boston Area are located at the State Co-operating Venereal Disease Clinics. Otherwise the penicillin request should be made to the Antitoxin and Vaccine Laboratory, 375 South Street, Jamaica Plain. Requests should be submitted to the nearest point of distribution.

For further information call the Division of Venereal Diseases, Department of Public Health, State House, Boston (CAPitol 4600).

## MISCELLANY

### NEW DEAN AT DARTMOUTH MEDICAL SCHOOL

Dr. Ernest M. Hopkins, president of Dartmouth College, recently announced the appointment of Dr. Rolf C. Syvertsen as dean of the Dartmouth Medical School, effective with the start of the new academic year on July 1. Dr. Syvertsen succeeds Dr. John P. Bowler, who, although he has resigned his administrative post, will continue on the medical faculty as professor of surgery.

Dr. Syvertsen, a graduate of Dartmouth in the class of 1918, will remain on the faculty as professor of anatomy. He was named assistant dean of the medical school last June, after filling the position of secretary for twenty years. He joined the medical school faculty in 1923, after serving as assistant in biology and zoology in the college for two years. He obtained his M.D. degree from Rush Medical College in 1936 and has held his professorship in anatomy since 1938.

### NEED FOR RED CROSS HOSPITAL WORKERS

Recognition of the outstanding contribution social workers are making in healing the emotional wounds of war has resulted in an unprecedented demand for their services.

The American Red Cross needs 750 trained social workers at once for supervisory, administrative and staff positions in military hospitals, largely in the United States. The wounded and disabled returned to this country for further treatment need the skilled help of trained and experienced social workers. New and higher salary schedules, ranging from \$170 to \$350 monthly, depending on education, experience and job assignment, have been adopted by the Red Cross. Quarters are provided, and if not available at the hospital, an additional allowance is made. Free uniforms are also issued.

In addition, 1650 untrained and partially trained workers are needed by the Red Cross to serve in the area of social case work under professional guidance. Salaries range from \$140 to \$200 monthly. The hospital program also calls for 600 recreation workers at monthly salaries of \$150 to \$325.

The project for which these 3000 hospital workers are being recruited will continue for many years. Despite this, however, employment will be offered by the Red Cross to any qualified worker willing to serve a minimum of one year. Applications should be filed at the nearest of the Red Cross area offices, which are as follows: North Atlantic Area, 300 Fourth Avenue, New York 10, New York; Eastern Area, 615 North St. Asaph Street, Alexandria, Virginia; Southeastern Area, 230 Spring Street, N. W., Atlantic 3, Georgia; Midwest Area, 1709 Washington Avenue, St. Louis 3, Missouri; and Pacific Area, Civic Auditorium, Larkin and Grove streets, San Francisco 1, California.

## NOTES

At its meeting on May 18, the New England Roentgen Ray Society paid honor to its distinguished member, Dr. George W. Holmes, pioneer radiologist and teacher, by establishing an annual lecture to be known as the George W. Holmes Annual Lecture.

Dr. Wesley Bourne of McGill University, Montreal, Canada, will deliver the first of the annual series of Osler Lectures of the University of Vermont College of Medicine at the Fleming Museum, Burlington, Vermont, July 5 and 6, at 8 p.m., and July 7, at 10 a.m. His subject will be "Anesthesia: Some contemplations."

## CORRESPONDENCE

### DEPRIVATION OF LICENSES

*To the Editor:* At a meeting of the Board of Registration in Medicine held June 6, the Board took the following actions:

To revoke the license of Dr. Julius Shubert, 45 McLean Street, Boston, to practice medicine for not less than three years because of gross misconduct in the practice of his profession as shown by collusion.

To suspend the license of Dr. Pasquale E. Massa, 252 Hanover Street, Boston, to practice medicine for a period of one year because of gross misconduct in the practice of his profession as shown by violation of the narcotic law and conspiracy to violate this law.

H. QUIMBY GALLUPE, M.D., *Secretary*  
Board of Registration in Medicine

State House  
Boston

### RESTORATION OF LICENSE

*To the Editor:* At a meeting of the Board of Registration in Medicine held June 6, the Board voted to restore the license to practice medicine in this Commonwealth of Dr. Ralph K. Coleman, 25 Fessenden Road, Arlington (formerly of Lowell).

H. QUIMBY GALLUPE, M.D., *Secretary*  
Board of Registration in Medicine

State House  
Boston

### THE FLINT FAMILY

*To the Editor:* In a letter published in the May 3 issue of the *Journal*, I made the suggestion that the Austin Flint referred to in the anecdote by the Reverend George Allen might have been a connection or even an ancestor of the two famous Austin Flint of New York City.

I have since learned that the latter is true and that Austin Flint, of Leicester, was the grandfather of the younger Austin Flint of New York City. The line is as follows:

Dr. Edward Flint, of Shrewsbury

↓  
Dr. Austin Flint, of Leicester (1760-1850)

↓  
Dr. Joseph H. Flint, of Leicester (1786-1846)

↓  
Dr. Austin Flint, of New York (1812-1886)

↓  
Dr. Austin Flint, of New York (1836-1915)

There were at least eight physicians in this family, and several of them lived to be ninety years of age, including Edward Flint, of Leicester, also a son of Austin Flint of Leicester.

Shrewsbury, Massachusetts

A. E. P. Rockwell, M.D.

## GIFTS OF MEDICAL BOOKS AND JOURNALS URGENTLY NEEDED FOR CZECHOSLOVAKIA

To the Editor: The Czechoslovak medical libraries and laboratories have been plundered by the Germans, and their research material wantonly destroyed. For the past six years no knowledge of the remarkable progress of American medicine has reached Czechoslovakia to benefit its people. Therefore a complete library of recent American medical literature is needed at the Charles University in Prague, as well as other universities and institutions. All publications since 1938 will be particularly welcome.

Any person or organization wishing to contribute is asked to communicate with the Secretary, American Friends of Czechoslovakia, 355 Boylston Street, Boston 16, or with the Masaryk Institute, 8 West 40th Street, New York City 18, which as a depository for Charles University in Prague receives and files donated publications.

MRS. J. PHILIP LANE, Secretary  
American Friends of Czechoslovakia

353 Boylston Street  
Boston 16

## BOOK REVIEWS

*The Religious and Philosophical Aspects of Van Helmont's Science and Medicine.* By Walter Pagel. 4°, paper, 44 pp. Baltimore: The Johns Hopkins Press, 1944. \$1.00. (Supplements to the Bulletin of the History of Medicine. Editor: Henry E. Sigerist, M.D.)

This book, written by an experienced historian of medicine, makes a valuable contribution to the further understanding of that great medical figure Johannes Baptista van Helmont, the *per ignem Philosophus*. Students of medicine must come to this book prepared for a hard intellectual feast, for it is not easy reading; they will, however, be repaid for their effort.

The research activities of van Helmont show a close interdependence of religious belief, philosophical outlook and scientific achievement. Modern students would do well to pry themselves free occasionally from the present-day sharp cleavage between science and religion to read of the works of a scientist who lived in an atmosphere where religious conviction constituted a strong incentive to scientific work, where only the God-fearing believed they could attain the art of prolonging life and where religious pragmatism was the driving force to medicine as the ultimate aim of science, all of which brings to mind the names of Pasteur, Charles Bell and Darwin. The author succeeds in showing why van Helmont, who introduced the concept of "gas," who designed scientific instruments, who used the balance in scientific quantitative experiments, who discovered acid as the principle of digestion in the stomach and laid the foundations for biochemistry and pathology, could deprecate sheer reasoning (*Ratio*) as a means for the investigation of life.

The book is provocative and should be in all medical libraries.

*The Gastro-Intestinal Tract: A handbook of roentgen diagnosis.* By Fred J. Hodges, M.D. 8°, cloth, 320 pp., with 130 plates. Chicago: The Year Book Publishers, Incorporated, 1944. \$5.50.

This is one of a series of books on roentgen diagnosis. It is short but represents a careful summary of the present knowledge of the gastrointestinal tract as determined by roentgenologic methods. The descriptive text shown on the left-hand pages is conveniently placed opposite excellent reproductions on the right. The text is brief, but within it is a large amount of useful information. There is a short but well-chosen bibliography at the close of each chapter. It should be of value to the student and also to the practitioner.

*Fertility in Women: Causes, diagnosis and treatment of impaired fertility.* By Samuel L. Siegler, M.D. With a foreword by Robert L. Dickinson, M.D. 8°, cloth, 450 pp., with 194 illustrations. Philadelphia: J. B. Lippincott Company, 1944. \$4.50.

This book is divided into eleven chapters. The first deals with the incidence of barrenness and the

evaluating and investigating fertility. The history subject matter of the third chapter, which also discusses causes of sterility, acquired and inherent, and points way to the detailed investigation of the subject. The physical examination comprises the fourth chapter, which brings special details in examination. In this chapter the illustrations are profuse, well chosen and well done. The physiology of the female sex cycle, taken up in the fifth chapter, presents an extensive review of the literature, together with the author's own views. The illustrations here, several in number together with numerous charts, make of the subject a reference work. In chapter six the cervical and vaginal secretions in relation to spermatozoa are discussed. In chapter seven methods of determining tubal patency and tubal occlusion are discussed and illustrated. The contention is made regardless of all the fallacies and objections to tubal ligation and hysterosalpingography, there is no doubting the efficacy of both procedures from the diagnostic and therapeutic standpoints in sterility and fertility; chapter eight treatment is elaborated. It deals with endocrine factor, genital hygiene, control of venereal diseases, premarital advice and examination, medical advice on fertility control, general treatment and specific treatment. The chapter presents a rather complete review of the treatment of ovarian imbalance — endocrine, irradiation and surgery. The treatment of faulty reception of the spermatozoa, many modalities, is reviewed in the tenth chapter, and artificial insemination is discussed. The author's views on the subject are sound and conservative, he being of the opinion that only a small percentage of the patients who apply for so radical a procedure. The concluding chapter deals with abortion in all its phases.

This well illustrated book presents an extensive bibliography, which in itself is a valuable contribution to the subject. It should serve not only as a textbook to the student of fertility but also as an important work of reference.

## NOTICES

### ANNOUNCEMENT

Dr. Joseph Igersheimer announces the removal of his office from 636 Beacon Street to 483 Beacon Street, Boston.

### MEDICOLEGAL CONFERENCE AND SEMINAR

During the first week in October the departments of medicine of the medical schools of Harvard, Tufts and Boston University, in association with the Massachusetts Medical Legal Society, will present a six-day program of lectures, conferences and demonstrations having to do with the investigation of deaths in the interests of public safety. Attendance during five of the six days of the course will be limited to fifteen persons who have registered in advance. On one day (October 3) the program will be open to any physician, lawyer, police official or senior medical student who may wish to attend. Further information may be obtained from the secretary of the Massachusetts Medico-Legal Society, 50 Shattuck Street, Boston 15.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 5

- FRIDAY, JULY 6  
\*9.00-10.00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.  
10.50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Mallory Building. Boston City Hospital.
- MONDAY, JULY 9  
\*12.00 m.-1.00 p.m. Clinicopathological conference. Peter I. Brigham Hospital.
- TUESDAY, JULY 10  
\*9.00-10.00 a.m. Medical clinic. Infants' Hospital.  
\*12.15-1.15 p.m. Clinicoroentgenological conference. Peter I. Brigham Hospital.
- WEDNESDAY, JULY 11  
\*12.00 m. Clinicopathological conference. Children's Hospital.
- \*Open to the medical profession.

SEPTEMBER 17. American Public Health Association. Page 752, in issue of November 30.  
OCTOBER 1-6. Medicolegal Conference and Seminar. Notice elsewhere.

